UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

Note to Reader
August 7, 1998

Background: As part of its effort to involve the public in the implementation of the Food Quality Protection Act of 1996 (FQPA), which is designed to ensure that the United States continues to have the safest and most abundant food supply, EPA is undertaking an effort to open public dockets on the organophosphate pesticides. These dockets will make available to all interested parties documents that were developed as part of the U.S. Environmental Protection Agency's process for making reregistration eligibility decisions and tolerance reassessments consistent with FQPA. The dockets include preliminary health assessments and, where available, ecological risk assessments conducted by EPA, rebuttals or corrections to the risk assessments submitted by chemical registrants, and the Agency's response to the registrants' submissions.

The analyses contained in this docket are preliminary in nature and represent the information available to EPA at the time they were prepared. Additional information may have been submitted to EPA which has not yet been incorporated into these analyses, and registrants or others may be developing relevant information. It's common and appropriate that new information and analyses will be used to revise and refine the evaluations contained in these dockets to make them more comprehensive and realistic. The Agency cautions against premature conclusions based on these preliminary assessments and against any use of information contained in these documents out of their full context. Throughout this process, if unacceptable risks are identified, EPA will act to reduce or eliminate the risks.

There is a 60 day comment period in which the public and all interested parties are invited to submit comments on the information in this docket. Comments should directly relate to this organophosphate and to the information and issues

available in the information in this docket. Once the comment period closes, EPA will review all comments and revise the risk assessments, as necessary.

These preliminary risk assessments represent an early stage in the process by which EPA is evaluating the regulatory requirements applicable to existing pesticides. Through this opportunity for notice and comment, the Agency hopes to advance the openness and scientific soundness underpinning its decisions. This process is designed to assure that America continues to enjoy the safest and most abundant food supply. Through implementation of EPA's tolerance reassessment program under the Food Quality Protection Act, the food supply will become even safer. Leading health experts recommend that all people eat a wide variety of foods, including at least five servings of fruits and vegetables a day.

Note: This sheet is provided to help the reader understand how refined and developed the pesticide file is as of the date prepared, what if any changes have occurred recently, and what new information, if any, is expected to be included in the analysis before decisions are made. **It is not meant to be a summary of all current information regarding the chemical.** Rather, the sheet provides some context to better understand the substantive material in the docket (RED chapters, registrant rebuttals, Agency responses to rebuttals, etc.) for this pesticide.

Further, in some cases, differences may be noted between the RED chapters and the Agency's comprehensive reports on the hazard identification information and safety factors for all organophosphates. In these cases, information in the comprehensive reports is the most current and will, barring the submission of more data that the Agency finds useful, be used in the risk assessments.

Jack Housenger, Acting Director
Special Review and Reregistration
Division

06/OPP#342

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MAR 26 1998

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

Certified Mail

RECEIVED
JUL 29 1998
OPP PUBLIC DOCKET

Robert E. Hawk
Gowan Chemical Company
P.O. Box 5569
Yuma, AZ 85366-5569

Subject: Bensulide Human Health Effects RED Chapter

Dear Mr. Hawk:

The Agency has completed its human health effects chapter for the bensulide RED document. A copy of the March 3, 1998, document is enclosed for your records. This chapter outlines several areas where the Agency is concerned about risks from the use of bensulide, including risks to agricultural workers and to those exposed through non-occupational uses of bensulide. The enclosed chapter discusses these risks in detail. Although this chapter also addresses the adequacy of the residue chemistry database, please disregard this section as the Agency is still reviewing your most recent residue chemistry proposal. You will receive a separate letter once the Agency completes this review. Please note that any risk reduction measures proposed in this chapter are intended to reduce the risk of bensulide used alone and do not include any measures to mitigate cumulative effects with other pesticides.

The Agency is providing you with thirty (30) days from the date of your receipt of this letter to submit any comments that you may have to this chapter. Please note that the Agency must receive your comments within the time frame provided to adequately address them in the final RED document. Comments received beyond the time frame provided may not be reviewed or addressed by the RED. If you have any questions regarding the reregistration of bensulide, please contact Susan Jennings at (703) 308-7130.

Sincerely,

Walter I. Waldrop
Reregistration Branch 3
Special Review and
Reregistration Division

Enclosure

(1)

March 3, 1998

MEMORANDUM

SUBJECT: The HED Chapter of the Reregistration Eligibility Decision Document (RED)
For Bensulide (Case 2035)

FROM: Raymond K. Locke, Team Leader (Toxicologist)
Reregistration Branch I
Health Effects Division (7509C)

THRU: Whang Phang, Ph.D., Senior Scientist
Registration Branch I
Health Effects Division (7509C)

TO: Susan Jennings/Walter Waldrop PM53
Reregistration Branch III
Special Review and Reregistration Division (7508W)

DP Barcodes: D238416, D238415
Submission Nos.: S528667, S528666
Case No.: 818572
Rereg. Case No.: 2035
P.C. Code: 009801
Tox. Chem. No.: 357

Please find attached the Human Health Assessment for the Bensulide Reregistration Eligibility Decision Document (RED). This chapter included the Hazard Assessment from Raymond Locke (Reregistration Branch I), the Product and Residue Chemistry Assessments from Catherine Eiden (Risk Characterization and Analysis Branch), the Occupational and Residential Exposure Assessment from Alan Nielsen (Reregistration Branch II) and Jeff Dawson (Reregistration Branch I), the Incidence Reports Data from Jerry Blondell (Chemistry and Exposure Branch II), the Dietary Risk Analysis from Brian Steinwand (Chemistry and Exposure Branch I) and Felicia Fort (Reregistration Branch I), and the Drinking Water Exposure Data (not used in this document) from William Effland, David Wells, and Stephanie Syslo (Environmental Risk Branch II/EFED).

Product and Use Information

Bensulide, S-(0,0-Diisopropyl phosphorodithioate) ester of N-(2-mercaptoethyl) benzenesulfonamide, is a selective organophosphate herbicide registered for a variety of terrestrial food crop, terrestrial non-food crop, and outdoor residential uses (classifications are based on LUIS report categories). Manufacturing-use products include the Gowan Company's 92% T and 46% FI; however, because bensulide is a List B chemical, only the 92% T/TGAI is subject to a reregistration eligibility decision. Bensulide is formulated as a technical-grade manufacturing product (92 percent active ingredient), three emulsifiable concentrate formulations (two at 4 and one at 6 pounds active ingredient per gallon), and as several granular formulations (3.6, 5.25, 7.0, 8.5, and 12.5 percent active ingredient). Emulsifiable concentrate (EC) products are labeled for use in all markets while granular products are labeled for use in only the terrestrial non-food and outdoor residential markets. The only product labelled for homeowner use is the 3.6G (Reg. No. 869-212).

Bensulide is currently registered for a wide variety of food uses . As a result of a 3-year storage stability study recently submitted by the registrant, tolerances for bensulide have been reassessed and an additional tolerance must be proposed for the Brassica (cole) vegetables group. Bensulide is also currently registered for use on turf (e.g., golf courses, schools, residential lawns).

Bensulide is applied as a pre-plant or pre-emergent herbicide in agricultural settings (i.e., to food crops) while non-food/outdoor residential applications (i.e., to turf and ornamentals) are made to established areas (e.g., lawns or golf course greens) prior to the emergence of the target plant species. "The herbicidal activity of bensulide is highly dependent on watering the material into the soil soon after application, so it is used almost entirely on irrigated crops and on turf into which it can be watered." Additionally, when applied pre-plant in agricultural settings, bensulide is generally soil incorporated. Bensulide can be applied by the use of chemigation, groundboom sprayers, handheld sprayers (low and high pressure devices and low pressure/high volume sprayguns commonly used on turf), backpack sprayers, tractor-drawn granular spreaders, push-type granular lawn spreaders, and bellygrinders. Aerial application is not precluded specifically on any bensulide label but correspondence from the registrant indicates that all agricultural applications of bensulide, the only scenario for which aerial applications seem appropriate, are completed only using ground equipment. Hence, exposures and risks associated with aerial application are not addressed in this document. Additionally, according to the registrant, greenhouse use and outdoor use "in commercial nurseries" is "negligible or nonexistent" even though labelling does not preclude this use pattern. Sod farm uses are also not apparently included on any label and are actually excluded by EPA Reg. No. 538-26. The aerial, greenhouse use, and sod farm scenarios should be addressed during label development to ensure that these use scenarios are not permitted without a further assessment. Bulk packaging is also used commercially for bensulide, particularly, in the desert southwest and the Rio Grande valley.

Product and Residue Chemistry

Most pertinent data requirements are satisfied for the bensulide 92% T/TGAI; however, additional data are required concerning OPPTS 830.1800 and 830.6313. In addition, data are required concerning UV/visible absorption for the PAI (OPPTS 830.7050). Provided that the registrant submits the data required in Table 1 for the 92% T, and either certifies that the suppliers of beginning materials and the manufacturing process for the bensulide TGAI have not changed since the last comprehensive product chemistry review or submits a complete updated product chemistry data package, HED has no objections to the reregistration of bensulide with respect to product chemistry data requirements. A tomato processing study must be submitted to fulfill the reregistration requirements for magnitude of the residue in the processed commodities of imported tomatoes.

In the Product and Residue Chemistry Chapters of the RED, HED recommends that tolerances for the following commodities: curcurbits, and leafy vegetables be revised from 0.1 ppm to 0.15 ppm to account for the instability of bensulide per se in/on these commodities as evidenced in a nonconcurrent storage stability study. In addition, the established tolerance for cottonseed should be revoked, because there are currently no registered uses of bensulide on cotton. Also, a tolerance must be proposed for the Brassica (cole) vegetables group. An appropriate level for this tolerance has been determined that reflects storage stability considerations, and A tolerance must be proposed for the Brassica (cole) vegetables group. An appropriate level for this tolerance has been determined that reflects storage stability considerations, and HED recommends the registrant propose a tolerance of 0.15 ppm.

Toxicology

Bensulide is classified under category IV for acute dermal toxicity and dermal irritation to the rabbit, category III for acute dermal and acute inhalation toxicity in the rat and primary eye irritation in the rabbit, and category II for acute oral toxicity in the rat. In addition, bensulide did not cause dermal sensitization in the guinea pig or acute delayed neurotoxicity in the hen.

As expected for an organophosphate herbicide, the most significant adverse toxicological effect of bensulide on non-target (non-plant) species is the inhibition of cholinesterase activities in blood plasma, red blood cells, and brain. Because there are no dermal absorption data available for bensulide, a dermal absorption of 20% was estimated from comparison of the oral and dermal acute toxicity studies in rats. However, HED is requesting single-dose dermal toxicity (GLN 81-2) and repeated-dose 21-day dermal toxicity (GLN 82-2) studies in rats to allow better estimate of the acute and short-term risks of dermal exposures to bensulide. HED requests that the registrant consult with HED for guidance with respect to the protocols to be used for these studies.

In the report (dated 7/31/97) of HED's Hazard ID Assessment Review Committee's meeting on bensulide, held on July 10, 1997, the following endpoints were identified for various periods of exposure, recommending the use of an MOE of 100 and an absorption value of 20% for dermal exposures:

Summary of Toxicological Endpoints for Bensulide

Exposure Duration	Expected Exposure Route	Endpoint and Toxicological Effect
Acute	Dietary	NOEL = 15 mg/kg, based on 80% inhibition of plasma cholinesterase activity in females on day 0 at 50 mg/kg (LOEL) in an oral (gavage) acute neurotoxicity study in rats (MRID 43195901)
Short-Term (1-7 days) Occupational/Residential	Dermal	NOEL = 5.5 mg/kg/day, based on a 48% decrease in maternal plasma cholinesterase activity at 23.0 mg/kg/day (LOEL) in an oral (gavage) developmental toxicity study in rats (MRIDs 00146585 and 92005018)
Intermediate-Term (one week to several months) Occupational/Residential	Dermal	NOEL = 0.5 mg/kg/day, based on a 57-58% reduction in plasma cholinesterase activity in both sexes and a 24% decrease in brain (pons) cholinesterase activity in males at 4.0 mg/kg/day (LOEL) in an oral (feeding) chronic (1-year) toxicity study in dogs (MRIDs 44066401 and 44052704; inhibition of plasma cholinesterase activities were observed in males and females at the earliest time point for measurements, 13 weeks)
All Time Periods	Inhalation	The highest dose tested in an acute inhalation toxicity test: LC_{50} (males and females)= 1.75±0.120 mg/L; this dose should be used, together with an assumption of 100% absorption via the inhalation route and estimates of expected inhalation exposure, to calculate the amount of bensulide expected to result from inhalation exposure. The inhalation risk should then be added to that expected from other routes of exposure to calculate the total risk for bensulide. (MRID 41646201)
Chronic (Non-Cancer) Occupational/ Residential (several months to lifetime)	Dermal and/or Dietary	NOEL = 0.5 mg/kg/day, based on a 57-58% reduction in plasma cholinesterase activity in both sexes and a 24% decrease in brain (pons) cholinesterase activity in males at 4.0 mg/kg/day (LOEL) in an oral (feeding) chronic (1-year) toxicity study in dogs (MRIDs 44066401 and 44052704); an estimated dermal absorption value of 20% should be used for dermal exposures.

The same report indicates that the Reference Dose (R_fD) for chronic oral exposure is 0.005 mg/kg/day, based on the NOEL from a one-year oral toxicity study in dogs [GLN 83-1(b); MRIDs 44066401 and 4405270]. At the next higher dose (4.0 mg/kg/day; LOEL), the following effects were observed: decreased (24% reduction) brain (pons) ChE activity in males, decreased (57-58% reduction) plasma cholinesterase activities in both sexes, and reduced body weight gain

(34% reduction) in females.

Additionally, the report indicates that the Committee classified Bensulide as a "Group E" substance, indicating evidence of non-carcinogenicity for humans; i.e., the chemical is not likely to be carcinogenic in humans via relevant routes of exposure. This weight of the evidence judgement is largely based on the absence of significant tumor increases in two adequate rodent carcinogenicity studies (rat and mouse). This classification is also supported by the lack of mutagenic activity.

Dietary Risk Analysis (Food)

Dietary Risk Evaluation System (DRES) acute and chronic exposure analyses were performed using the reassessed tolerance level residues and 100 percent crop treated information to estimate the Theoretical Maximum Residue Contribution (TMRC) for the general population and 22 subgroups. These analyses revealed that both the acute and chronic dietary risks from ingestion of bensulide-treated food are of minimal concern for all population subgroups.

Occupational and Residential Exposure

There are bensulide products registered for both homeowner (outside the scope of the Worker Protection Standard) and occupational uses (within the scope of WPS). Risks due to occupational or residential exposure to bensulide are both unacceptable (note that, due to lack of data, the oxygen analogue was not considered in this assessment).

Occupational Risks:

- Even with the imposition of engineering controls, the MOEs for several of the exposure scenarios for pesticide handlers are below 100 for both short- and intermediate-term dermal exposures.

- Non-dietary hand-to-mouth exposures were not considered in this assessment, due to the overwhelming magnitude of dermal exposures.

- There is minimal concern for handler risks due to inhalation exposures, since the MOE's calculated for such exposures without the use of Personal Protective Equipment (PPE) or engineering controls are well above 100. Additionally, there is minimal concern for post-application reisks due to inhalation exposures because of the low vapor of bensulide.

- Post-application exposures are not expected from agricultural uses, due to cultivation practices that are anticipated with this preplant/pre-emergent herbicide. Calculated MOEs do not fall below 100 until 36 to 62 days post-application for occupational turf management scenarios, depending upon application rate.

- Chronic exposure to bensulide is not anticipated by any route of exposure for any scenario.

Non-Occupational and Residential Risks:

- For persons dermally exposed to bensulide-treated turf (e.g., golfers on treated greens, children or adults on treated residential lawns), both short-term and intermediate-term risks exceed HED's level of concern.

- Chronic exposure to bensulide is not anticipated by any route of exposure for any scenario.

- Inhalation non-occupational risks are considered to be minimal (for reasons described above for occupational risks).

Recommendations for mitigation of these occupational, non-occupational, and residential risks will require meeting with the registrant.

FQPA Considerations

With respect to special sensitivity to infants and children, HED recommends, on the basis of results from acceptable toxicology studies, that the additional 10x safety factor be removed for the following reasons: 1) no increased sensitivity to fetuses was observed as compared to maternal animals following an acute *in utero* exposure in developmental studies in rats and rabbits, and 2) no increased sensitivity was observed to pups as compared to adults in a multi-generation reproduction study in rats.

cc: R. Locke (RRBI)
C. Eiden (RCAB)
A. Nielsen (RRBII)
J. Dawson (RRBI)
J. Bondell (CEBII)
B. Steinwand (CEBI)
F. Fort (RRBI)
W. Effland (ERBII/EFED)
D. Wells (ERBII/EFED)
S. Syslo (ERBII/EFED)

BENSULIDE: HEALTH EFFECTS DIVISION'S (HED's)
CHAPTER FOR THE REREGISTRATION ELIGIBILITY DECISION DOCUMENT

Risk Assessor: Raymond K. Locke (Toxicologist)_____
Reregistration Branch I
Health Effects Division (7509C)

Senior Scientist: Whang Phang, Ph.D._____
Reregistration Branch I
Health Effects Division (7509C)

Branch Chief: Michael S. Metzger_____
Reregistration Branch I
Health Effects Division (7509C)

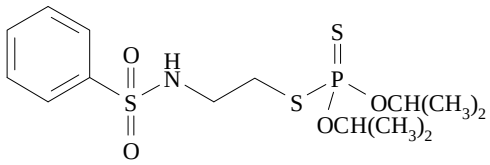
II. EXECUTIVE SUMMARY

III. SCIENCE ASSESSMENT

A. Physical and Chemical Properties Assessment

DESCRIPTION OF CHEMICAL

Bensulide [S-(O,O-diisopropyl phosphorodithioate) ester of N-(2-mercaptoethyl) benzenesulfonamide] is an herbicide registered for food/feed uses on Brassica leafy vegetables, carrots, cucurbits, fruiting vegetables, leafy vegetables, garlic, dry bulb onions, and shallots.



Empirical Formula:	$C_{14}H_{24}NO_4PS_3$
Molecular Weight:	397.5
CAS Registry No.:	741-58-2
Shaughnessy No.:	009801

IDENTIFICATION OF ACTIVE INGREDIENT

Pure bensulide is a colorless solid with a melting point of 34.4°C. Technical bensulide is a viscous amber liquid at temperatures above 34°C and a solid below this temperature. Bensulide is soluble in water at 25 ppm at 20°C and is miscible with acetone, ethanol, 4-methylpentan-2-one, and xylene.

MANUFACTURING-USE PRODUCTS

A search of the Reference Files System (REFS) conducted 4/15/97 identified two bensulide manufacturing-use products (MPs) registered under Shaughnessy No. 009801: the Gowan Company 92% T and 46% FI (EPA Reg. Nos. 10163-201 and 10163-202). Because bensulide is a List B chemical, only the 92% T/TGAI is subject to a reregistration eligibility decision.

REGULATORY BACKGROUND

The current status of the product chemistry data requirements for the bensulide technical product is presented in Table 1. Refer to this table for a listing of the outstanding product chemistry data

requirements.

Case Name: Bensulide
Registrant: Gowan Company
Product(s): 92% T (EPA Reg. No. 10163-201)

TABLE 1: PRODUCT CHEMISTRY DATA SUMMARY

Guideline Number	Requirement	Are Data Requirements Fulfilled? [1]	MRID Number [2]
830.1550	Product Identity and Disclosure of Ingredients	Y [3]	00088284 [4], 00163310 [4], 42685001 [5], CSF 2/26/93 [6]
830.1600 830.1620 830.1650	Starting Materials and Manufacturing Process	Y	00163310
830.1670	Discussion of Formation of Impurities	Y	00163310
830.1700	Preliminary Analysis	Y	00163299, 40033501
830.1750	Certification of Ingredient Limits	Y	00163299, CSF 2/26/93 [6]
830.1800	Analytical Methods to Verify the Certified Limits	N [7]	00163299, 40033501
830.6302	Color	Y	41532001
830.6303	Physical State	Y	41532001
830.6304	Odor	Y	00157314
830.6313	Stability	N [8]	41532001
830.7000	pH	Y	41532001
830.7050	UV/Visible Absorption	N [9]	
830.7200	Melting Point/Melting Range	Y	41532001
830.7220	Boiling Point/Boiling Range	N/A [10]	
830.7300	Density/Relative Density/Bulk Density	Y	41532001 [4], 42685001 [5]
830.7370	Dissociation Constant in Water	N/A [11]	41532001
830.7550 830.7560 830.7570	Partition Coefficient (Octanol/Water)	Y	00157314
830.7840 830.7860	Solubility	Y	41532001
830.7950	Vapor Pressure	Y	41532001

[1] Y = Yes; N = No; N/A = Not Applicable.

[2] References reviewed under CBRS No. TBA, DP Barcode TBA, currently under review, unless otherwise noted.

[3] We note that the label claim of 92% is not in agreement with the nominal concentration of the active ingredient listed on the CSF.

[4] CBRS No. 9532, D173998, 9/15/92, F. Fort.

[5] CBRS No. 11574, D189279, 4/22/93, K. Dockter.

[6] The CSF was obtained from the product jacket.

[7] Supporting validation data are required for the analytical methods used for the quantitation of three impurities present at ≥0.1%.

[8] Data reflecting the stability of the TGAI on exposure to metals and metal ions are required.

[9] The OPPTS Series 830, Product Properties Test Guidelines provide guidance on determining UV/visible absorption for the PAI, proposed (Draft 40 CFR Part 158) to be required.

[10] Data are not required because the TGAI is a solid at room temperature.

[11] Data are not required because bensulide is not an acid or a base.

CONCLUSIONS

Most pertinent data requirements are satisfied for the bensulide 92% T/TGAI; however, additional data are required concerning OPPTS 830.1800 and 830.6313. In addition, data are required concerning UV/visible absorption for the PAI (OPPTS 830.7050). Provided that the registrant submits the data required in Table 1 for the 92% T, and either certifies that the suppliers of beginning materials and the manufacturing process for the bensulide TGAI have not changed since the last comprehensive product chemistry review or submits a complete updated product chemistry data package, HED has no objections to the reregistration of bensulide with respect to product chemistry data requirements. A tomato processing study must be submitted to fulfill the reregistration requirements for magnitude of the residue in the processed commodities of imported tomatoes.

B. HUMAN RISK ASSESSMENT

1. HAZARD ASSESSMENT

Toxicology data are used by HED to assess the hazards to humans and domestic animals. The data are derived from a variety of acute, subchronic, and chronic toxicity tests; developmental/ reproductive tests; and tests to assess mutagenicity and pesticide metabolism. Reregistration

eligibility decisions require that HED have sufficient information to select the appropriate end-points for performing a human health risk assessment. This requires a toxicological database that is not only complete, but of acceptable quality.

The toxicity database for bensulide is complete and will support a reregistration eligibility determination for the currently registered uses.

1.a. Acute Toxicity (81-Series)

Table 2 summarizes the acute toxicity of bensulide, technical grade, by different routes of exposure. The purity of the bensulide used in these studies ranged from 92.4 to 93.8 percent.

TABLE 2: Acute Toxicity Values of Technical Bensulide

TEST	RESULT	TOXICITY CATEGORY
Oral LD_{50} in rat (MRID No.: 00097921 and 92005011) Date 2/21/78	LD_{50} = Males: 360 (315-411) mg/kg Females: 270 (238-306) mg/kg Acceptable/Guideline	II
Dermal LD_{50} in rat (MRID No.: 41597501) Date 5/18/89	LD_{50} = > 2000 mg/kg (limit test) Males and females Acceptable/Guideline	III
Dermal LD_{50}; in rabbit (MRID No.: 00097921) Date 2/21/78	LD_{50} > 5000 mg/kg (limit test) Males and females Acceptable/Guideline	IV
Inhalation LC_{50} in rat (MRID No.: 41646201) Date 5/17/89	LC_{50} > 1.75 ± 0.120 mg/L Males and females Acceptable/Guideline	III
Eye irritation in rabbit (MRID No.: 41597502) Date 5/17/89	Mild irritant, causing mild conjunctival irritation [slight redness (6/6 animals); slight to severe discharge (5/6); no corneal or iridial effects] clearing within three days Acceptable/Guideline	III
Dermal irritation in rabbit (MRID Nos.: 00097921 and 92005012) Date 2/21/78	Mild irritant; primary dermal irritation index = 0.5	IV

Dermal sensitization in guinea pig (MRID No.: 00160075) Date 5/20/86	Not a sensitizer; did not cause dermal irritation. Acceptable/Guideline	N/A[a]
Acute delayed neurotoxicity in hen (MRID Nos.: 43306301 and 43334302) Date 7/12/94	Did not induce delayed neurotoxicity in the hen. Acceptable/Guideline	N/A
Acute oral neurotoxicity in rat (MRID No.: 43195901) Date 5/23/94	NOEL for neurotoxicity = 100 mg/kg, based on flaccid abdominal and/or body tone and pinpoint pupils in females at 150 mg/kg (LOEL). The plasma cholinesterase (ChE) inhibition LOEL is 50 mg/kg, based on 80% inhibition (no p) of plasma cholinesterase activity in females on Day 0. The plasma ChE NOEL is 15 mg/kg. The RBC ChE inhibition LOEL is 150 mg/kg, based on 37% inhibition ($p \leq 0.01$) of RBC ChE activity in females on Day 0. The RBC ChE NOEL is 50 mg/kg. The brain ChE inhibition LOEL is 150 mg/kg, based on 18% inhibition (no p) of brain ChE activity in females on Day 0 and 27% inhibition ($p \leq 0.01$) on Day 15. The brain ChE NOEL is 50 mg/kg. Acceptable/Guideline	N/A

[a]Not applicable

1.b. Subchronic Toxicity

GLN 82-2/21-Day Dermal Toxicity (Rat):

In a 21-day dermal toxicity study (MRID 42162002), male and female specific pathogen-free Wistar-derived albino rats (Alpk:APfSD strain; 5/sex/dose; 6-8 weeks old) were dermally treated over a 5 cm x 10 cm area of clipped dorso-lumbar skin with bensulide technical (92.7% a.i.) at dose levels of 0 (sham control), 10, 100, and 1000 mg/kg/day (limit test dose). Dosing occurred 21 times over a period of 30 days (five days/week). Following each dosing, the application site

was covered with an occlusive dressing (gauze patch, a patch of plastic film secured by adhesive bandages, and two pieces of 2.5 cm-wide PVC tape wrapped around the animals) for approximately 6 hours. After each 6-hour exposure period, the dressings were removed and the application sites washed with warm water. On dosing days, animals were fitted with Elizabethan collars to prevent test substance ingestion. Rats were observed for clinical signs and dermal irritation prior to dosing, after each removal of dressings, and at least once daily during non-dosing days. They were weighed daily, and food consumption was recorded twice weekly. At study termination, cardiac blood samples were collected shortly after animal sacrifice for hematological and clinical chemistry determinations. Gross necropsies were conducted, the standard set of organs were fixed for potential histopathology, and the following organs were also weighed: adrenals, brain, kidneys, liver, and testes (males). Only the kidneys of all animals, and the treated and untreated skins and livers of the control (0 mg/kg/day) and high-dose (1000 mg/kg/day) were examined histologically.

There were no deaths, compound-related clinical signs, or significant changes in body weight or food consumption in any group. A small incidence of dermal trauma was apparently caused by the bandages. No abnormal hematology was seen, and the only clinical chemistry anomaly was a 43% decrease in plasma triglycerides in the high-dose (1000 mg/kg/day) males compared to controls; females were not affected. In the absence of other findings, this decrease is of unknown biological significance. There were no dose-related gross lesions or organ weight changes. Some scabbing of treated and untreated skin, due to bandage trauma, was observed in all groups. This observation correlates with several histopathologic findings of slight to minimal acanthosis, parakeratosis, and inflammatory infiltration in treated and untreated skin. A number of minimal to slight renal lesions were observed, but they are not clinically significant and may have represented artifacts. Therefore, the NOEL is > 1000 mg/kg/day (limit dose), based on the lack of any observed toxicity, and the LOEL was not determined.

This study was classified as Acceptable/Guideline and satisfies the Guideline requirement for a 21-day dermal toxicity study (82-2) in the rat.

GLN 82-1/90-Day Subchronic Toxicity (Rat):

In a subchronic toxicity study (MRID 43919601), male and female Sprague-Dawley rats (10/sex/dose) were given bensulide (92.4% a.i.) in the diet for 13 weeks at doses of 0, 5, 15, 45, or 100 mg/kg/day.

Significantly decreased body weight gains ($p<0.01$, 19%) were observed for male rats at 100 mg/kg/day. Although not significant, body weight gains for female rats were 12, 11, and 14% lower than controls at 15, 45, and 100 mg/kg/day, respectively. Food consumption appeared not affected by treatment. Overall food efficiency was decreased in males at 100 mg/kg/day.

Significantly increased alanine amino-transferase levels were observed at 45 mg/kg/day (87% increase in males; 48%, females) and 100 mg/kg/day (145%, males and 90%, females). Dose-related inhibition of ChE activity occurred in both sexes. Relative to controls, plasma ChE

decreases were 28, 54, and 62% (males) at 15, 45, and 100 mg/kg/day, respectively, and 19, 47, 84, and 90% (females) at 5, 15, 45, and 100 mg/kg/day, respectively. Red blood cell ChE decreases were 47 and 59% (males) and 38 and 66% (females) at 45 and 100 mg/kg, respectively. Brain ChE decreases were 18 and 43% (males) at 15 and 100 mg/kg/day, respectively, and 28 and 58% (females) at 45 and 100 mg/kg, respectively. Increased relative liver weights were observed in males (17%, $p<0.01$) and females (19%, $p<0.001$) at 100 mg/kg/day. The hepatic toxicity was corroborated by mild histological changes in the liver in males (fatty microvesicles at 100 mg/kg/day; vacuolation at 45 and 100 mg/kg/day).

Under the conditions of this study, the NOEL is 5 mg/kg/day; the LOEL is 15 mg/kg/day, based on decreased plasma ChE activity in both sexes, decreased brain ChE activity in males, and an equivocal reduction in body weight gain in females.

This subchronic dietary toxicity study in rats is classified as Acceptable/Guideline and satisfies the guideline requirements (§82-1a) for a subchronic toxicity study in the rat.

GLN 82-1/13-Week Feeding Study in Dogs:

In a 13-week subchronic toxicity study (MRID 44052703), bensulide (92.4% a.i., Lot #CBI 0801) was administered via the diet to four dogs/sex/group at dose levels of 0, 1, 3, 10, or 30 mg/kg/day for 13 weeks.

Activated partial thromboplastin times were prolonged in both sexes in the 30 mg/kg/day treatment group at 6 and 13 weeks and in females in the 10 mg/kg/day group at 13 weeks. At 1 mg/kg/day, plasma cholinesterase activities were 38.2 and 22.4% lower in male and female dogs, respectively, at 13 weeks compared to the controls. In the 3, 10, and 30 mg/kg/day treatment groups at 13 weeks, plasma cholinesterase activities were reduced by 61-79% in males and 30-78% in females. Red cell cholinesterase activities in the 30 mg/kg/day group were 12.4% lower for males and 22.4% lower in females at 13 weeks, but these differences were not statistically significant. Pons cholinesterase activities were unchanged by treatment, but cerebellum cholinesterase activities were decreased 35.8% (not statistically significant) in the 30 mg/kg/day group females after 13 weeks of test article administration.

Males in the 1, 10 and 30 mg/kg/day treatment groups had increased absolute (13-19%) and relative (17-22%) liver weights and females in the 30 mg/kg/day treatment group also had increased absolute (20%) and relative (19%) liver weights. Lipid deposits were found in the hepatocytes of 1/4 males in the 3 mg/kg/day treatment group, 1/4 males and 1/4 females in the 10 mg/kg/day group, and 4/4 males and 4/4 females in the 30 mg/kg/day treatment group. No other treatment-related effects were observed. Mean body weights, body weight gains, and food consumption values were similar in all groups. No neoplastic tissue was observed. The LOEL for this study is 1 mg/kg/day, based on the reduction in plasma cholinesterase activities in both sexes and increased absolute and relative liver weights in males at this dose level. A NOEL was not established.

This 13-week subchronic toxicity study is classified Acceptable/Guideline and does meet the guideline requirement for a subchronic oral toxicity study in dogs (§82-1b).

1.c. Chronic Toxicity/Carcinogenicity (83-series guidelines)

GLN 83-5/2-Year Combined Chronic Toxicity/Oncogenicity Study in Rats:

In a combined chronic/oncogenicity study (MRIDS 43919602 and 44161101), bensulide (92.4 ±0.5% a.i., Lot # CBI 0801) was administered in the diet for 104 weeks to 80 Sprague-Dawley rats/sex/group at levels to achieve constant weekly doses of 0, 1, 15, or 60 mg/kg/day. At approximately the 26, 52, and 78 week intervals, 10 rats/sex/group were terminated, and all remaining animals were sacrificed at 104 weeks of the study.

Survival rates, ophthalmoscopic findings, clinical observations, hematological parameters, urinalysis findings, and gross findings were unaffected by treatment with bensulide. Chronic toxicity in rats receiving 60 mg/kg/day was characterized in both sexes by reduced ($p \leq 0.05$, <0.01 or <0.001) cholinesterase levels (plasma, ↓59-93%; erythrocyte, ↓44-80%; and brain, ↓20-39%) and, in the males, by increased absolute liver weights (↑4-22%) and mild histopathological changes of the liver (hepatocyte vacuolation and eosinophilic foci). In the 15 mg/kg/day animals, reduced ($p<0.05$, <0.01, or 0.001) plasma (↓36-73%) and erythrocyte (↓20-40%) cholinesterase activities were also observed.

The chronic LOEL is 15 mg/kg/day based on inhibition of plasma and erythrocyte cholinesterase activity in the mid- and high-dose group animals, inhibition of brain cholinesterase activity in the high-dose animals, and increased liver weights and mild histopathological changes in the high-dose males. The chronic NOEL is 1 mg/kg/day.

Under the conditions of this study, there was no evidence of carcinogenic potential.

Dosing was considered adequate by decreased cholinesterase activity (plasma, red blood cell, and brain) in high-dose animals and by increased absolute liver weights and liver histopathological changes in the high-dose males.

This study is classified as Acceptable/Guideline and satisfies the guideline requirements for a chronic toxicity study (§83-1) and a carcinogenicity study (§83-2) in the rat.

GLN 83-2/18-Month Carcinogenicity Study in Mice:

In a mouse oncogenicity study (MRID 44161105), bensulide (92.4 ±0.5% a.i., Lot # CBI 0801) was administered for 78 weeks in the diet to 50 CD-1 mice/sex/dose at levels to achieve constant weekly doses of 0, 1, 50, or 200 mg/kg/day. An additional 10 mice/sex/dose were used to provide samples for plasma and red blood cell cholinesterase assessments at 13 weeks, and further cholinesterase assessments, including brain cholinesterase at 52 weeks; these animals were terminated and discarded at 52 weeks. All remaining animals were sacrificed at 78 weeks of the

study.

Survival rates, clinical observations, and hematological parameters were unaffected by treatment with bensulide. Chronic toxicity was characterized by reduced ($p<0.01$ or <0.001) cholinesterase levels (plasma, ↓92-96%; erythrocyte, ↓40-51%) in the high-dose males and females and reduced brain cholinesterase in the high-dose females (↓14%). Additionally in the high-dose males, decreased overall body weight gains (↓32%; $p<0.001$), increased absolute and relative liver weights (↑38-43%; $p<0.001$), and histopathological changes of the liver (pale foci, cell atypia, and cell foci) were observed. In the 50 mg/kg/day animals, reduced ($p<0.01$, or 0.001) plasma (↓88-92%) and RBC (↓31-37%) cholinesterase activities were observed and brain cholinesterase activity was reduced (↓12%; $p<0.05$) in the females. Additionally, overall body weight gain in the mid-dose males was reduced by 16% ($p<0.05$) compared to controls.

The chronic LOEL is 50 mg/kg/day based on inhibition of plasma and erythrocyte cholinesterase activity in the 50 and 200 mg/kg/day group animals, inhibition of brain cholinesterase activity in the mid- and high-dose females, decreased body weight gain in the mid- and high-dose males, and increased liver weights, and histopathological changes in the high-dose males. The chronic NOEL is 1 mg/kg/day.

Under the conditions of this study, there was no evidence of carcinogenic potential.

Dosing was considered adequate based on decreased plasma, RBC, and brain cholinesterase activities, decreased body weight gains, and by increased liver weights and histopathological changes of the liver.

This study is classified as Acceptable/Guideline and satisfies the guideline requirements for a carcinogenicity study (§83-2b) in mice.

GLN 83-1/1-Year Feeding Study in Dogs:

In a chronic toxicity study (MRID 44066401), bensulide (92.4% a.i.) was administered to four dogs/sex/dose by feeding at dose levels of 0, 0.5, 4, or 30 mg/kg/day for 52 weeks. Analytical determinations demonstrated actual bensulide concentrations to be within ± 10% of theoretical values throughout the study. Additional analytical data (MRID 44052704) verified the adequacy of the homogeneity and stability of bensulide in the test diets.

In the 30 mg/kg/day treatment group, there was a 66-73% reduction in plasma cholinesterase activities, a 18.7-35.5% reduction in brain (pons) cholinesterase activities, and a 32-45% reduction in red cell cholinesterase activities. In addition, in the high-dose females, mean body weight gains were 52% lower than the controls and histopathological changes were observed in the liver. Focal accumulations of pigmented Kupffer cells were observed in 2/4 females, and mild cytoplasmic vacuolation was noted in 3/4 females in the 30 mg/kg/day group. Absolute weights of the adrenal glands of males in the 30 mg/kg/day treatment group were 29% higher than the controls. In the 4 mg/kg/day treatment group, there was a 57-58% reduction in plasma

cholinesterase activity, a 24% reduction in brain (pons) cholinesterase activities (males only), and a 34% reduction in body weight gain (females only). In the 0.5 mg/kg/day treatment group, only sporadic reductions in plasma cholinesterase activity were observed in males and females compared to the controls. No animals died during the course of the study, and no treatment-related changes were observed in their appearance or behavior. Food consumption appeared to be unaffected by treatment. No ocular, hematological, or urine abnormalities were detected during the study. No neoplastic tissue was observed in dogs in the treatment and control groups. The LOEL for this study is 4 mg/kg/day, based on the reduced body weight gains in females, reduced (24%) brain (pons) cholinesterase activity in males, and a 57-58% reduction in plasma cholinesterase activities in both sexes. The NOEL is 0.5 mg/kg/day.

This chronic toxicity (feeding) study in dogs is classified Acceptable/Guideline and satisfies the guideline requirement for a chronic toxicity study in nonrodents (§83-1b).

1.d. Developmental Toxicity

GLN 83-3/Developmental Toxicity Study (Rat):

In a developmental toxicity study (MRID 00146585), bensulide technical (92.8 % a.i.) was administered to 25 or 26 female Sprague-Dawley rats/dose in corn oil by gavage at analytically determined dose levels of 0, 5.5, 23.0 or 95.0 mg/kg/day from days 6 through 20 of gestation.

Bensulide technical exerted no effects on maternal gross pathology, fertility, or cesarian parameters. The maternal systemic LOEL is 95.0 mg/kg/day (HDT), based on tremors, decreased body weight (range: 93-94% of control value) on days 12, 16, and 21 of gestation, decreased body weight gain during days 9-12 (25% control value) and 6-21 (76% of control value) of gestation, decreased (79% of control value) feed intake during days 13-16 of gestation, and decreased whole and corrected (reproductive tract subtracted) body weights (93% and 91% of control values, respectively) and increased liver/body weight ratio (112% of control value) at study termination. The maternal systemic NOEL is 23.0 mg/kg/day (MDT).

The Maternal NOEL for cholinesterase inhibition is 5.5 mg/kg/day (LDT), based on a 48% decrease in plasma ChE activity at 23.0 mg/kg/day (LOEL; MDT) in the absence of any other effects.

The Developmental NOEL $\geq$ 95.0 mg/kg/day (HDT), based on the lack of any developmental effects. The developmental LOEL > 95.0 mg/kg/day.

This developmental toxicity study in the rat is classified Acceptable/Guideline and does satisfy the guideline requirement for a developmental toxicity study (§83-3a) in the rat.

GLN 83-3/Developmental Toxicity Study (Rabbit):

In a developmental toxicity study (MRID 00152845), inseminated New Zealand White rabbits,

randomly assigned to one control and three treatment groups of 18 animals each, were administered Betasan® (bensulide technical; 92.8% a.i.) by oral gavage at doses of 0, 5, 20, or 80 mg/kg/day on gestation days (GD) 7-19, inclusive. Cesarean section examinations were performed on all surviving does on GD 29, followed by teratological examination of all fetuses.

No treatment-related effects were observed in the 5 or 20 mg/kg/day groups as compared with controls. Three high-dose animals aborted, one each on GD 18, 27, and 28, and were sacrificed and necropsied. All other animals survived until scheduled sacrifice. Decreased defecation was observed in 3, 2, 1, and 11 animals and decreased urination was observed in 3, 2, 0, and 11 animals in the control, 5, 20, and 80 mg/kg/day groups, respectively. No other dose- or treatment-related clinical signs of toxicity were observed during the study. Maternal body weight gains were significantly ($p \leq 0.05$ or 0.01) less in the high-dose group as compared to the controls throughout the dosing interval with an overall weight loss recorded during the treatment interval. Absolute body weights of the high-dose animals were less than the controls beginning on GD 13 but statistical significance ($p \leq 0.01$) was reached only on GD 19. After cessation of treatment, does in the high-dose group showed recovery with body weight gains significantly ($p \leq 0.01$) greater than the controls. During the dosing interval, food consumption by the high-dose animals was significantly ($p \leq 0.01$) less than the control beginning on GD 10. Overall food consumption was significantly less in the high-dose group for the entire dosing interval (62%; $p \leq 0.01$) and the entire gestation period (83%; $p \leq 0.05$) as compared to controls.

Therefore, the maternal toxicity NOEL is 20 mg/kg/day and the maternal toxicity LOEL is 80 mg/kg/day based on reduced body weights and weight loss during the treatment interval.

There were no differences between treated and control groups for live fetuses/litter, fetal body weights, or fetal sex ratios. No treatment-related malformations/variations were observed for any external, visceral, or skeletal parameter examined of kits in the treated litters as compared to the control litters. There was no difference in the total number of litters containing fetuses with major malformations as compared to controls: 3/15, 1/15, 0/10, and 2/10 affected in the control, 5, 20, and 80 mg/kg/day groups, respectively.

Therefore, the developmental toxicity NOEL is $\geq$80 mg/kg/day and the developmental toxicity LOEL was not identified.

This developmental toxicity study in rabbits is classified as Acceptable/Guideline and satisfies the guideline requirement (§83-3b) for a developmental toxicity study in rabbits.

1.e. Reproductive Toxicity

GLN 83-4/2-Generation Study of Reproduction (Rat):

In a two-generation reproduction study (MRID 43948701), Bensulide (92.4% a.i.; Lot No. CDI 0801) was administered to male and female Sprague-Dawley CD rats in the diet at concentrations of 0, 25, 150, or 900 ppm for two generations. Premating doses for the F_0 males were 2.0, 12.3,

and 68.2 mg/kg, respectively, and for the F_0 females were 2.3, 13.2, and 80.8 mg/kg, respectively. Premating doses for the F_1 males were 2.3, 14.0, and 86.5 mg/kg, respectively, and for the F_1 females were 2.6, 15.4, and 93.2 mg/kg, respectively. The F_0 generation contained 28 animals/sex/dose and the F_1 generation contained 24 animals/sex/dose. Animals were given test or control diet for at least 10 weeks then mated within the same dose group. F_1 animals were weaned on the same diet as their parents. At least 21 litters were produced in each generation. All animals were exposed to test material either in the diet or during lactation until sacrifice.

Although several deaths occurred among treated and control groups of both generations, these were considered incidental to treatment. No overt treatment-related clinical signs of toxicity were observed in the adult animals of either sex or generation. There were no statistically significant differences between treated and control groups of either sex or generation for absolute body weights, body weight gains, food consumption, or gross or histopathological findings.

Therefore, the NOEL for systemic effects $\geq$ 900 ppm (82.8 mg/kg/day; HDT) and the LOEL was not determined.

Terminal cholinesterase activity was measured in plasma, red blood cell, and brains of the adult animals of both generations. Baseline or pretreatment activities were not measured. In F_0 males, plasma cholinesterase activity was significantly ($p \leq 0.01$) reduced in the mid- and high-dose groups as compared to controls with percent inhibition (%I) 21 and 54%, respectively. High-dose F_0 males also had significantly ($p \leq 0.01$) reduced RBC activity (%I = 32). Mid- and high-dose F_0 females had significantly ($p \leq 0.01$) reduced plasma activity (%I = 43 and 76, respectively) while high-dose F_0 females also had significantly ($p \leq 0.01$) reduced RBC (%I = 57) and brain (%I = 68) activities. Plasma activity was significantly ($p \leq 0.01$) reduced in all treated F_1 male groups as compared to controls (%I = 28, 30, and 62, respectively). Mid- ($p \leq 0.05$) and high-dose ($p \leq 0.01$) F_1 males also had significantly reduced RBC activity (%I = 11 and 42, respectively). Mid- and high-dose F_1 females had significantly ($p \leq 0.01$) reduced plasma activity (%I = 47 and 80, respectively) while high-dose F_1 females also had significantly ($p \leq 0.01$) reduced RBC and brain activities (%I = 63 and 51). The 51-68% inhibition of brain ChE activity in females in the high-dose (900 ppm) group indicates that dosing was conducted at an adequately high level; higher doses would likely yield an unacceptable level of mortality.

Therefore, the LOEL for cholinesterase inhibition is 25 ppm (2.3 mg/kg/day; LDT) based on inhibition of plasma enzyme activity in F_1 males. The cholinesterase inhibition NOEL was not identified.

No statistically significant differences occurred for absolute body weights, body weight gains, or food consumption of the F_0 or F_1 females during gestation or lactation for any treated group as compared to controls. High-dose F_0 males and females had low fertility indices with only 21 of 28 males siring litters and only 24 of 28 females becoming pregnant. However, this effect was not repeated in the F_1 generation. There were no statistically significant differences between treated and control groups for number of litters or pups/litter during lactation of either generation. Survival and viability of the F_1 pups was similar between treated and control groups. However,

survival was greatly reduced in the high-dose F_2 pups with overall (day 0-21) survival only 61%. This was due mainly to a low viability index of 74% for lactation days 0-4.

Therefore, the LOEL for reproductive toxicity is 900 ppm (93.2 mg/kg/day; HDT) based on reduced F_2 pup survival. The corresponding NOEL for reproductive toxicity is 150 ppm (15.4 mg/kg/day; MDT).

This study is classified as Acceptable/Guideline and does satisfy the guideline requirement for a reproduction study (§83-4) in rats.

1.f. Mutagenicity

The available studies clearly indicate that bensulide is not genotoxic. Additionally, the negative mutagenicity studies support the lack of an oncogenic effect in the rat and mouse long-term feeding studies and also the absence of significant reproductive or developmental toxicity attributable to a mutagenic mode of action (i.e., decreased total implants, increased resorptions). Based on the overall results, there is no concern for mutagenicity.

The submitted test battery satisfies the new mutagenicity initial testing battery guidelines; therefore, no Category III study or additional further testing is required at this time.

GLN 84-2/Mutagenicity (Category I):

In a reverse gene mutation assay in bacteria (MRID 00153493), strains TA98, TA100, TA1535, and TA1537 of S. typhimurium were exposed to bensulide technical (92.9% a.i.) at concentrations of 0 (dimethyl sulfoxide solvent control; DMSO), 0.005, 0.014, 0.041, 0.123, 0.370, 1.111, 3.333, 10.000, 25.000, or 50.000 μL/plate (TA100) or 0 (DMSO), 0.037, 0.111, 0.333, 1.000, or 3.000 µL/plate (TA98, TA1535, and TA1537) in the presence and absence of mammalian metabolic activation (metabolic activation mixture containing the S9 fraction from livers of Aroclor 1254-induced Sprague-Dawley rats).

Bensulide technical was tested up to and above levels at which it precipitated onto the culture medium ($\geq$ 0.041 µL/plate for TA100; $\geq$ 1.000 µL/plate for TA98, TA1535, and TA1537). The positive controls did induce the appropriate responses in the corresponding strains. There was no evidence of induced mutant colonies over background.

This study is classified as Acceptable/Guideline. It does satisfy the requirement for Guideline 84-2 for in vitro mutagenicity (bacterial reverse gene mutation) data.

GLN 84-2/Mutagenicity (Category I):

In a mammalian cell gene mutation assay (TK locus; MRID 43273901), mouse lymphoma

L5178Y cultured cells cultured in vitro were exposed to bensulide technical (92.4 ± 0.5% a.i.; given in MRID 43919602) in dimethyl sulfoxide (DMSO) at concentrations of 8, 14, 16, 21, 24, 28, 32, 35, 40, or 42 µg/mL in the absence and at 16, 24, 28, 32, 35, 40, 42, 48, 49, or 56 µg/mL in the presence of mammalian metabolic activation (S9 fraction containing homogenate from Aroclor 1254-induced rat liver).

Bensulide technical was tested up to cytotoxic concentrations, based on preliminary cytotoxicity assays demonstrating significant cytotoxicity at doses near 30 µg/mL and total cell death at doses as low as 25-30 µg/mL. There was no evidence of induced forward mutation at the TK locus over solvent control values at any dose tested.

This study is classified as Acceptable/Guideline. It does satisfy the requirement for Guideline 84-2 for in vitro mutagenicity (gene mutation in mammalian cells) data.

GLN 84-2/Mutagenicity (Category II):

In a C57BL/6JfCD-1/Alpk mouse bone marrow micronucleus assay (MRID 41902602), 5 animals/sex/dose were treated with a single oral (gavage) dose of bensulide technical (92.7% a.i.) in corn oil (vehicle) at doses of 250 or 400 mg/kg (constant dose volume of 10 mL/kg). Bone marrow cells were harvested at 24, 48 and 78 hours post-treatment.

There were no signs of toxicity during the study. Bensulide technical was tested at an adequate dose, since the 400 mg/kg dose level (HDT) was selected based on the results of a preliminary acute toxicity study (2 animals/sex/dose) in which mortalities were observed at doses of 500 mg/kg or greater, but not at 400 mg/kg or less. The positive control (cyclophosphamide) induced the appropriate response. There was no significant increase in the frequency of micronucleated polychromatic erythrocytes in bone marrow after any treatment time.

This study is classified as Acceptable/Guideline. It does satisfy the requirement for Guideline 84-2 for in vivo mutagenicity (mouse bone marrow micronucleus) data.

1.g. General Metabolism (85-series guidelines)

GLN 85-1/Metabolism and Pharmacokinetics:

In a metabolism study (MRIDs 42007901-42007904), bensulide technical, labelled with ^{14}C in the phenyl ring (> 96.4% radiopurity; 925 MBq/mMole) was dissolved in corn oil (vehicle) and administered to Sprague-Dawley rats (5/sex/group; 7-8 weeks of age; 185-235 g body weight) following three treatment regimes. Animals in Group I received a single oral dose of radioactive bensulide at 1 mg/kg of body weight. Animals in Group II received 14 consecutive doses (1 mg/kg/day) of non-radioactive bensulide technical (99% a.i.) in corn oil, followed by a 1 mg/kg dose of radiolabelled bensulide technical in corn oil on day 15. Group III animals received a single oral dose of radiolabelled bensulide technical at 100 mg/kg of body weight. An additional group of animals (Group IV; 3/sex/group) were given a single oral dose of radiolabelled bensulide

technical at 1 mg/kg of body weight and were subseqently used for autoradiological radiolabelled carbon dioxide release determinations. Administration by gavage was used for all treatment groups, and the volume of the corn oil and bensulide technical solution was kept at a constant of 4mL/kg of body weight.

For animals in Groups I-III, urine and feces were collected at 12, 24, 36, and 48 hours post-dosing and at 24-hour intervals thereafter until 7 days after dosing with radioactive bensulide. All animals in Groups I-III were sacrificed 7 days after treatment with radioactive bensulide technical, and the following organs were removed and assayed for radioactivity: blood, liver, kidneys, muscle, fat lungs, uterus, heart, bone, spleen, thyroid, salivary glands, brain, adrenals, ovaries, testes, pancreas, gastrointestinal tract (stomach, small and large intestines, and caecum) and its contents, and the residual carcass. Radioactivity was determined by tissue combustion and/or liquid scintillation counting. For Groups IV animals, two rats of each sex were used for the autoradiography study and 1 rat of each sex was used or the carbon dioxide study.

In the autoradiography study, animals were sacrificed with Halothane at 24 hours after dosing with radioactive bensulide technical. The animals were then immediately frozen in a mixture of hexane and solid carbon dioxide. Each frozen carcass was embedded in a block of 2% carboxymethyl cellulose, and longitudinal sagittal section of about 20 µM thickness were cut and representative sections freeze-dried and subjected to autoradiography. In the carbon dioxide study, ^{14}C-radiolabelled derived from the metabolism of radioactive bensulide technical and present in expired air was collected by passing the air through a 2N NaOH solution at 6, 12, 24, 36, and 48 hours after dosing.

The major route of excretion was via the urine, with peak urinary excretion of ^{14}C-bensulide equivalents occurring between 0 to 24 hours for males and females in the low-dose group (Group I; 1 mg/kg) and in the high-dose group (Group III; 100 mg/kg). In Group I, total urinary excretion of 7 days after administration of radioactive bensulide technical accounted for 70 and 75 percent of the administered dose in males and females, respectively. Of these totals, 57 and 72 percent were excreted during the first 24 hours after dosing for males and females, respectively. In Group III, total urinary excretion accounted for 75 and 87 percent of the administered dose in males and females, respectively. Of these totals, 64 and 76 percent were excreted during the first 24 hours after dosing for males and females, respectively. For Group II (prior 14-day administration of non-radioactive bensulide technical before radioactive bensulide administration, both at 1 mg/kg), total urinary excretion of radioactivity over 7 days past dosing with radioactive bensulide accounted for 79 and 88 percent of the administered dose in males and females, respectively. Of these totals, 63 and 83 percent were excreted during the first 24 hours after dosing for males and females, respectively. For Group IV, urinary excretion of ^{14}-C radioactivity derived from bensulide technical over a 48-hour period accounted for 67% for one male and 86% in one male.

For Group I, total fecal excretion of radioactivity derived from ^{14}C-bensulide technical over 7 days post-dosing accounted for 22 and 20 percent of the administered dose in males and females, respectively. Of these totals, 18 percent was excreted during the first 24 hours for both males and

females. For Group III, total fecal elimination over 7 days post-dosing of bensulide-derived radioactivity accounted for 22 and 11 percent of the administered dose for males and females, respectively. Of these totals, 20 and 8 percent were excreted during the first 24 hours after dosing for males and females, respectively. In Group II animals, total fecal excretion of radioactivity over 7 days post-dosing accounted for 14 and 8 percent of the administered dose for males and females, respectively. Of these totals, 9 and 6 percent were excreted during the first 24 hours post-dosing for males and females, respectively. In Group IV, fecal excretion of radioactivity over 48 hours post-dosing accounted for 12% of the administered dose in one male and 7% in one female.

The amount of residual radioactivity in all organs/tissues except for the liver (0.02 to 0.21% of the dose) from all rats was low at 7 days after single oral administration of radioactive bensulide technical. The radioactivity found in the carcasses and in other tissues accounted for 0.3% to 2.5% and less than 0.1% of the administered dose, respectively. The highest concentration of radioactivity was found in whole blood. The majority of the radioactivity in the blood was associated with the cellular component. In general, less well perfused tissues showed lower concentrations of radioactivity. Whole body autoradiography of rats killed 24 hours after dosing showed that, in male rats, the majority of the radioactivity was present in the blood, lung, spleen, bone marrow, and the glandular part of the stomach, the contents of the intestines, and in the intestinal walls. Moderate amounts of radioactivity was found in the liver, kidney, salivary glands, the capsule of the seminal vesicles, nasal passages and the white matter of the brain. The intensity of radioactivity in the female rats was much lower than in the male rats.

These studies are acceptable; however, by themselves, they do not satisfy the Guideline (§85-1) requirements for metabolism data for bensulide technical in rats because these studies are limited to the tissue distribution and excretion of orally administered ^{14}C-bensulide. Additional information on the biotransformation of bensulide (the identification of the urinary and fecal metabolites of bensulide) in rats are required.

In a biotransformation study (MRID 42225401), bensulide metabolites were quantitated and identified in rat urine and fecal extracts from previous studies (MRID 42007901-42007903). To obtain sufficient material to confirm metabolite identities, four successive daily doses of 50 mg [^{14}C]-bensulide/kg were administered to 5 Sprague-Dawley female rats (bulk collection experiment; 99% a.i., unlabeled, Batch No. Y06379/006; >98.0% a.i., [^{14}C]-labeled, Batch No. Y06379/005). Biliary excretion was assessed in one male and one female rat with cannulated bile ducts given an oral dose of 100 mg [^{14}C]-bensulide/kg.

No animals died before scheduled sacrifice in either experiment. In the bulk collection experiment, 52.5% of the administered dose was recovered in the urine and 16.3% in the feces. In cannulated rats, a substantially higher fraction of the given dose was in the feces (40.9% in the male, 68.6% in the female), possibly due to poor intestinal wall absorption. Biliary excretion was minimal (5-6% of dose) and biliary metabolites were not analyzed; the mass balance accounting was acceptable (109.2%-114.4%).

Bensulide metabolites found by TLC in excreta from previous studies accounted for about 59-78% of the administered dose in the urine and about 2.5-8.3% in the feces, distribution varying with sex and dose. Four metabolites were identified. Metabolite I was the most abundant in the urine for all doses in both sexes (26-58% of given dose) whereas in fecal extracts, Metabolites I, II, or IV predominated (each 0.25-3.4% of dose). Unidentified metabolites individually represented < 3% of the dose except urinary metabolite "H" (≤ 16.1% of dose) and one fecal metabolite (TLC spot 6; ≤ 6.23% of dose). Metabolite I and II formation is proposed to involve cleavage of the $PO_2[CH(CH_3)_2]_2$ moiety of bensulide, followed by methylation and oxidation of the sulphur atom. Conjugation with glycine or carboxylation and oxidative desulphuration is proposed to lead to Metabolite III and IV formation, respectively.

This supplemental study is classified as unacceptable (Non-Guideline) but is upgradable. It was intended to satisfy the guideline requirement for a metabolism study (§85-1) in rats together with four previous studies (MRIDs 42007901-42007904). The study is upgradable, if the registrant submits data showing reasonable efforts were made to identify urinary metabolite "H," which represents 5.6-16.1% of the administered dose; an additional study is not required.

1.h. Neurotoxicity

GLN 81-7/Delayed Neurotoxicity in the Hen:

In an acute delayed neurotoxicity study (MRID 43334302), Bensulide (tech., 92.4% a.i.) was assessed using groups of 15 single comb white leghorn laying hens (*Gallus gallus domesticus*) given a single neat gavage dose of Bensulide (2000 mg a.i./kg nominal dose; actual dose was 2262 mg/kg in a dosing volume of 2 mL/kg). An acute oral toxicity study (43306301) determined an LD_{50} of 3221 mg/kg for Bensulide in the domestic laying hen. Positive controls (12 birds) were given 800 mg TOCP/kg and 12 birds given corn oil served as vehicle controls. Three birds of each group were sacrificed at ~48 hrs for activity analysis of neurotoxic esterase (NTE) in brain and spinal cord and acetylcholinesterase (AChE) in brain. Behavior assessments (locomotor ability) were conducted on nine birds from both control groups and 12 birds from the Bensulide group over a period of 21 days. Pathology (brain, spinal column and peripheral nerves) was evaluated in all remaining animals at Day 21.

Based on the study results, Bensulide did not induce acute delayed neurotoxicity in the domestic laying hen at the dose tested. NTE activity was not affected by treatment. A non-significant decrease of ~24% was observed for brain cholinesterase in treated hens.

This study meets the requirements of § 81-7 and is classified as Acceptable/Guideline because, although animals were not tested at the LD_{50} and no signs of neurotoxicity were observed, animals were tested at the limit dose of 2 g/kg.

GLN 81-8ss/Acute Neurotoxicity in the Rat:

In an acute neurotoxicity screening study (MRID 43195901), 22 CD rats/sex/group were

administered single gavage doses of 0, 30, 100 or 300 mg bensulide (tech., 92.4% a.i.)/kg (males) or 0, 15, 50 or 150 mg/kg (females) in 5 mL/kg corn oil. Functional observational battery (FOB) and motor activity tests were conducted on 12 rats/sex/dose pretreatment, on the day of dosing (day 0) and days 7 and 14 post-dosing. Plasma, erythrocyte and brain cholinesterase (ChE) activities were measured from 5 rats/sex at pretreatment, day 0 (6.25 and 6.75 hrs post-dosing) and day 15. Six perfused control and high dose rats/sex were evaluated for neuropathology.

At 150 mg/kg (females only), an increased incidence of diarrhea, flaccid abdominal and/or body tone (all 6/12 vs. 1, 2 and 2, controls) and pinpoint pupils (3/12 vs 0, controls) were observed on Day 0 in the FOB. At 300 mg/kg (males only), one death occurred on Day 1, preceded by clinical signs (salivation, lacrimation/ocular discharge, decreased respiration, hypothermia, and fur staining on muzzle and ventral surface). A second male exhibited abnormal respiration, tremors, hypoactivity, dehydration and fur staining between Days 1-3. In the FOB, increased incidence of decreased arousal and locomotor activity (for both, 7/12 vs. 3, controls) were observed. A slight but statistically significant depression of body weight (-6.6%) was also observed on Day 7. No treatment-related effects on motor activity or macroscopic/microscopic neuropathology were reported. The LOEL is 150 mg/kg, based on minimal, transient clinical signs consistent with cholinesterase inhibition in females. The NOEL is 100 mg/kg.

At 50 mg/kg (females only), plasma ChE was decreased on day 0 by 80% less than controls (not significant). At 100 mg/kg (males only), plasma ChE was decreased on day 0 by 53% (not significant). At 150 mg/kg (females only) on day 0, reductions were observed in plasma ChE (89% less than controls, $p<0.01$) and erythrocyte ChE (37% less than control, $p<0.01$) both of which showed partial recovery by day 15. However, a significant decrease (73% of control, $p<0.01$) in brain ChE for high-dose females was noted on day 15 which was not present at day 0 (18% less than controls, not significant). At 300 mg/kg (males only), statistically significant ChE inhibition was observed only in the high-dose groups. On day 0, there were significant decreases in brain ChE (62% of control, $p<0.01$), plasma ChE (19% of control, $p<0.01$), and erythrocyte ChE (60% of control, $p<0.01$) for males of the high dose (300 mg/kg) group. At day 15, brain ChE was still significantly reduced (73% of control, $p<0.01$) but values for plasma and erythrocyte ChE had returned to normal.

> The plasma ChE inhibition LOEL is 50 mg/kg, based on 80% inhibition (no p) of plasma cholinesterase activity in females on Day 0. The plasma ChE NOEL is 15 mg/kg.
>
> The RBC ChE inhibition LOEL is 150 mg/kg, based on 37% inhibition ($p \leq 0.01$) of RBC ChE activity in females on Day 0. The RBC ChE NOEL is 50 mg/kg.
>
> The brain ChE inhibition LOEL is 150 mg/kg, based on 18% inhibition (no p) of brain ChE activity in females on Day 0 and 27% inhibition ($p \leq 0.01$) on Day 15. The brain ChE NOEL is 50 mg/kg.

This study is classified as Acceptable/Guideline and satisfies the guideline requirement for an acute neurotoxicity study in rats (§81-8ss).

2. DOSE/RESPONSE ASSESSMENT

2.a. Special Sensitivity to Infants and Children

Adequacy of the data base: The toxicology data base on bensulide includes an acceptable two-generation reproduction study in rats (MRID 43948701) and acceptable prenatal developmental toxicity studies in rats (MRID 00146585) and rabbits (MRID 00152845), meeting the basic data requirements, as defined for a food-use chemical by 40 CFR Part 158. No data gaps were identified.

Susceptibility issues: The toxicology data provided no indication of increased sensitivity of rats or rabbits to *in utero* and/or postnatal exposure to bensulide. In the two-generation reproduction study in rats, cholinesterase inhibition (ChEI) in the adult animals was observed at a dose which produced no evidence of toxicity in the offspring (the parental plasma ChEI NOEL was <2.3 mg/kg/day, while the offspring NOEL was 15.4 mg/kg/day, based on decreased viability in second generation pups at 93.2 mg/kg/day, the highest dose tested). In both the prenatal developmental toxicity studies in rats and rabbits, developmental toxicity was not observed up to the highest dose tested, although evidence of systemic toxicity was demonstrated in the maternal animals, including body weight decrements in both species and tremors, decreased food consumption, increased liver weights, and cholinesterase inhibition in rats.

The developmental toxicity studies are designed to evaluate adverse effects on the developing organism resulting from pesticide exposure during prenatal development. Reproduction studies provide information relating to effects from exposure to the pesticide on the reproductive capability of mating animals. Based on its developmental and reproductive database, the Agency has concluded that, although bensulide elicited decreased viability in second generation pups at the highest dose tested in the reproduction study, this result, when considered together with the negative results in two developmental studies, does not raise concerns regarding the adequacy of the standard uncertainty factor.

Therefore, the Health Effects Division Hazard Identification Assessment Review Committee decided at a meeting held on July 10, 1997, that the additional 10x factor (as required by FQPA) should be removed, since the toxicology data indicated: 1) no increased sensitivity to fetuses as compared to maternal animals following an acute *in utero* exposure in developmental studies in rats and rabbits, and 2) no increased sensitivity to pups as compared to adults in a multi-generation reproduction study in rats.

2.b. Reference Dose (RfD)

The Health Effects Division Hazard Identification Assessment Review Committee met on July 10, 1997, to discuss and evaluate the toxicology data base in support of bensulide reregistration and to reassess the Reference Dose (R_fD) for this chemical. The R_fD was established at 0.005 mg/kg/day, and was based on the NOEL from a one-year oral toxicity study in dogs [Guideline

83-1(b); MRIDs 44066401 and 4405270] for decreased (24% reduction) brain (pons) ChE activity in males, decreased (57-58% reduction) plasma cholinesterase activities in both sexes, and reduced body weight gain (34% reduction) in females observed at 4.0 mg/kg/day (LOEL) and the standard uncertainty factor (UF) of 100 to account for both the interspecies extrapolation and intraspecies variability.

NOEL for critical study: 0.5 mg/kg/day, based on decreased (24% reduction) brain (pons) ChE activity in males, decreased (57-58% reduction) plasma cholinesterase activities in both sexes, and reduced body weight gain (34% reduction) in females observed at 4.0 mg/kg/day (LOEL).

2.c. Carcinogenic Classification and Risk Quantification

The Health Effects Division Hazard Identification Assessment Review Committee met on July 10, 1997, to discuss and evaluate the oncogenicity data base in support of bensulide reregistration and to reassess the cancer classification of this chemical. The Committee classified Bensulide as a "Group E" substance, indicating evidence of non-carcinogenicity for humans; i.e., the chemical is not likely to be carcinogenic in humans via relevant routes of exposure. This weight of the evidence judgement is largely based on the absence of significant tumor increases in two adequate rodent carcinogenicity studies (rat: MRID Nos.: 43919602, 44161101, 44161102, 44161103, and 44206301; mouse: MRID Nos.: 44161102, 44161103, 44161104, 44161105, and 44206301). This classification is also supported by the lack of mutagenic activity (MRIDs 00153493, 41902601, 41902602, 42479201, 43273901, 470065014, 470065015, and 470065016). It should be noted, however, that designation of an agent as being in Group E is based on the available evidence and should not be interpreted as a definitive conclusion that the agent will not be a carcinogen under any circumstances.

2.d. Developmental Classification

Bensulide has been shown to elicit no developmental effects at the highest doses tested in studies in both rats (95 mg/kg/day; MRID 00146585) and rabbits (80 mg/kg/day; MRID 00152845). Therefore, it is not regarded as a developmental toxicant.

2.e. Dermal Absorption

There are no dermal absorption data available for bensulide. The only dermal studies conducted with bensulide consist of acute dermal toxicity studies in the rat (MRID 41597501) and rabbit (MRID 00097921) and a 21-day dermal toxicity study in the rat (MRID 42162002). None of these studies included determinations of the effect of bensulide on the activities of cholinesterase enzymes present in blood plasma, red blood cells, or brain. However, an apparent dermal absorption value of 20% can be estimated for bensulide from studies conducted with the rat (rabbit data should not be used, since bensulide is a thioate organophosphate which must be activated to the oxon and it is well known that the rabbit is significantly insensitive to the effects of organophosphates which require activation).

If an acute LD_{50} value has been determined for a pesticide by the dermal and oral routes in the same species and sex, then one may estimate the percent dermal absorption. One assumes that 100% of the pesticide is absorbed by the oral route at the oral LD_{50} to produce the systemic dose that elicits the toxic effect (death of one-half of the animals on test) and that the same systemic dose is produced at the dermal LD_{50}. Three criteria must be met to use this approach meaningfully: 1) test materials of essentially the same composition and purity (in this case, technical bensulide) must be used for both the oral and dermal studies; 2) the same species and sex must be used to assure that similar metabolic processes occur in each test (the rat is the preferred species for organophosphates requiring activation); and 3) the same toxicological endpoint (in this case, the death of one-half of the animals on test) must be used in both the dermal and oral tests. The acute LD_{50} toxicity studies of bensulide by the oral (MRIDs 00097921 and 92005011) and dermal (MRID 41597501) routes satisfy these criteria; therefore an estimate of the percent dermal absorption at the LD_{50}s may be calculated as:

$$\text{Estimated Percent Absorbed} = \frac{\text{Oral } LD_{50} \text{ in mg/kg of body weight}}{\text{Dermal } LD_{50} \text{ in mg/kg of body weight}} \text{ X } 100$$

In the acute oral toxicity study in rats (MRIDs 00097921 and 92005011), the observed LD_{50} values were 270 mg/kg for females and 360 mg/kg for males, indicating that females were more sensitive to the acute lethality effects of bensulide. In the acute dermal toxicity study in rats (MRID 41597501), the observed LD_{50} for both males and females was greater than the highest dose tested (> 2000 mg/kg; represents a limit dose).

Using these observed LD_{50} values, the following estimated dermal absorption percentages may be calculated:

$$\text{Males: } \frac{360 \text{ mg/kg}}{>2000 \text{ mg/kg}} = < 18\%$$

$$\text{Females: } \frac{270 \text{ mg/kg}}{>2000 \text{ mg/kg}} = < 13.5\%$$

Given the uncertainties underlying these estimates, an upper limit estimate of 20% dermal absorption for bensulide is suggested as a first approximation for use in risk assessment. It should be noted that this estimate is most useful for clinical signs of toxicity, and might have limited value with respect to cholinesterase inhibition. A more meaningful estimate of dermal absorption for use in risk assessments for inhibition of cholinesterase activities could be obtained with data from a single-dose acute toxicity study and a 21-day dermal toxicity study using female (most sensitive sex) rats which included determinations of the effects of bensulide on cholinesterase activities in blood plasma, red blood cells, and brain.

2.f. Other Toxicological Endpoints

A summary of the toxicological endpoints chosen for risk assessments of exposure to bensulide for various time periods by appropriate routes of exposure is presented in Table 3.

i. Acute Dietary (One Day)

Study Selected - Guideline No.: 81-8ss, Acute neurotoxicity in the rat

MRID No.: 43195901

Executive Summary: See section III.B.1.a. for a review of this study.

Dose and Endpoint for use in risk assessment: Inhibition of plasma ChE activity in females on Day 0.

NOEL = 15 mg/kg, based on 80% inhibition of plasma cholinesterase activity in females on Day 0 at 50 mg/kg (LOEL).

Comments about study and/or endpoint: This risk assessment is required. Since the NOEL/LOEL for calculating the MOE was taken from plasma cholinesterase inhibition observed in an oral acute neurotoxicity study, the appropriate population sub-group for estimating the acute dietary risk for bensulide is all subgroups, and a standard MOE of 100 should be used, together with an estimated dermal absorption value of 20%.

ii. Short Term Occupational and Residential (1-7 Days)

Critical Study: Developmental Toxicity study in rats (83-3a), MRID Nos. 00146585, and 92005018

Executive Summary: See section III.B.1.d. for a review of this study.

Endpoint and Dose Level selected for use in risk assessment: NOEL = 5.5 mg/kg/day, based on inhibition of maternal plasma cholinesterase activity (48%) at 23.0 mg/kg/day (LOEL).

Comments: This risk assessment is required. A 21-day dermal toxicity study in Wistar rats (MRID No. 42162002) was available. However, since cholinesterase measurements were not performed, and no adverse effects were observed, this study could not be used in the risk assessment for this exposure category. Since the NOEL/LOEL for calculating the MOE was taken from maternal plasma cholinesterase inhibition observed in an oral developmental toxicity study in rats, the appropriate population sub-group for estimating the short-term risk for bensulide is all population subgroups, using the standard MOE of 100, and an estimated dermal absorption value of 20%.

iii. Intermediate Term Occupational and Residential (One Week to Several Months)

Critical Study: 83-1(b), Chronic toxicity study in the dog (83-1b), MRID Nos. 44066401, and 44052704.

Executive Summary: See section III.B.1.c. for a review of this study.

Endpoint and Dose Level Selected for Use in Risk Assessment: NOEL = 0.5 mg/kg/day based on inhibition of plasma cholinesterase activity in both sexes and brain cholinesterase activity in males at 4.0 mg/kg/day (LOEL).

Comments: This risk assessment is required. The endpoint from this oral chronic study is applicable to intermediate-term occupational or residential exposure, since at the earliest time point at which measurements were taken (13 weeks), plasma cholinesterase was decreased 57% ($p \leq 0.001$) in males and 56% ($p \leq 0.01$) in females at the 4.0 mg/kg/day dose level. Since the NOEL/LOEL for calculating the MOE was taken from plasma and brain cholinesterase inhibition observed in an oral chronic toxicity study in dogs, the appropriate population sub-group for estimating the intermediate-term risk for bensulide is all population subgroups and the standard MOE of 100 and an estimated dermal absorption value of 20% should be used.

iv. Chronic (Non-Cancer) Occupational and Residential (Several Months to Lifetime)

Critical Study: Chronic toxicity study in the dog (83-1b), MRID Nos. 44066401 and 44052704

Executive Summary: See section III.B.1.c. for a review of this study.

Endpoint and Dose Selected for Use in Risk Assessment: NOEL = 0.5 mg/kg/day, based on inhibition of plasma cholinesterase activity in both sexes and brain cholinesterase activity in males at 4.0 mg/kg/day (LOEL).

Comments: This risk assessment is required, if chronic occupational or residential exposure is identified. Since the NOEL/LOEL for calculating the MOE was taken from plasma and brain cholinesterase inhibition observed in an oral chronic toxicity study in dogs, the appropriate population sub-group for estimating the chronic risk for bensulide is all population subgroups, using the standard MOE of 100. Since this is an oral study, an estimated dermal absorption value of 20% should be used for dermal exposure.

v. Inhalation Exposure (Variable Duration)

Critical Study: Acute inhalation toxicity in the rat (81-3), MRID No. 41646201

Executive Summary: See section III.B.1.a. for the results from this study.

Endpoint and Dose Level selected for use in risk assessment: 1.75 ± 0.102 mg/L, the only dose level tested in this acute inhalation toxicity test. This represents a dose of 244.4 mg/kg/day for

males and 219.9 mg/kg/day for females (see Appendix I).

Comments: This risk assessment is required. It is recommended that the highest dose tested in the acute inhalation toxicity study be used with the assumption of 100% absorption via the inhalation route and estimates of expected inhalation exposure, to calculate the amount of bensulide expected to result from inhalation exposure. The estimated inhalation risk should then be added to the risks expected from other routes of exposure to calculate the aggregate risk for bensulide.

TABLE 3: Summary of Toxicological Endpoints for Bensulide

Exposure Duration	Expected Exposure Route	Endpoint and Toxicological Effect
Acute	Dietary	NOEL = 15 mg/kg, based on 80% inhibition of plasma cholinesterase activity in females on day 0 at 50 mg/kg (LOEL) in an oral (gavage) acute neurotoxicity study in rats (MRID 43195901)
Short-Term (1-7 days) Occupational/Residential	Dermal	NOEL = 5.5 mg/kg/day, based on a 48% decrease in maternal plasma cholinesterase activity at 23.0 mg/kg/day (LOEL) in an oral (gavage) developmental toxicity study in rats (MRIDs 00146585 and 92005018)
Intermediate-Term (one week to several months) Occupational/Residential	Dermal	NOEL = 0.5 mg/kg/day, based on a 57-58% reduction in plasma cholinesterase activity in both sexes and a 24% decrease in brain (pons) cholinesterase activity in males at 4.0 mg/kg/day (LOEL) in an oral (feeding) chronic (1-year) toxicity study in dogs (MRIDs 44066401 and 44052704; inhibition of plasma cholinesterase activities were observed in males and females at the earliest time point for measurements, 13 weeks)

All Time Periods	Inhalation	The highest dose tested in an acute inhalation toxicity test: LC_{50} (males and females)= 1.75±0.120 mg/L; this dose should be used, together with an assumption of 100% absorption via the inhalation route and estimates of expected inhalation exposure, to calculate the amount of bensulide expected to result from inhalation exposure. The estimated inhalation risk should then be added to the risks expected from other routes of exposure to calculate the aggregate risk for bensulide. (MRID 41646201)
Chronic (Non-Cancer) Occupational/ Residential (several months to lifetime)	Dermal and/or Dietary	NOEL = 0.5 mg/kg/day, based on a 57-58% reduction in plasma cholinesterase activity in both sexes and a 24% decrease in brain (pons) cholinesterase activity in males at 4.0 mg/kg/day (LOEL) in an oral (feeding) chronic (1-year) toxicity study in dogs (MRIDs 44066401 and 44052704); an estimated dermal absorption value of 20% should be used for dermal exposures.

3. DIETARY EXPOSURE AND RISK ASSESSMENT/CHARACTERIZATION

3.a. Dietary Exposure (Food Sources)

i. GLN 860.1200: Directions for Use

A Reference Files System (REFS) search, conducted on 05/16/97, identified two bensulide end-use products (EPs) registered under Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Section 3 to Gowan Company, with registered uses on food/feed crops. These EPs, including the associated Special Local Need (SLN) registrations under FIFRA Section 24 (c), are listed in Table 4.

For the purpose of generating this Residue Chemistry Science Chapter, HED examined the registered food/feed use patterns and reevaluated the available residue chemistry database for adequacy in supporting these use patterns.

Table 4: Bensulide EPs with Food/Feed Uses Registered to Gowan Company.

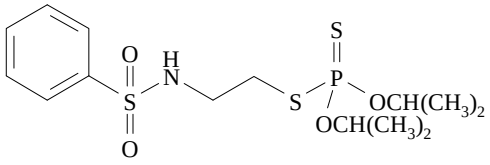
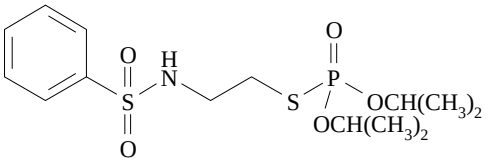
EPA Reg. No.	Label Acceptance Date	Formulation	Product Name
10163-200 [1]	04/16/97	4 lb/gal EC	Prefar® 4-E Selective Herbicide
10163-222 [2]	04/16/97	6 lb/gal EC	Prefar® 6-E Selective Herbicide

[1] Including SLN Nos. AZ940001, ID930008, OR940023, and WA940010.
[2] Including SLN Nos. CA970001 and OR960040.

ii. GLN 860.1300: Nature of the Residue - Plants

The reregistration requirements for plant metabolism are fulfilled. Acceptable studies depicting the qualitative nature of the residue in carrots, lettuce, and tomatoes have been submitted and evaluated. The cottonseed metabolism study requested in the Phase 4 Review is no longer required because cotton has been removed from the registrant's product labels. The bensulide residues of concern are those that are currently regulated, bensulide and bensulide oxygen analog (see Figure 1).

Figure 1. Chemical Names and Structures of Bensulide Residues of Concern in Plant Commodities.

Common Name Chemical Structure Chemical Name	**Common Name** Chemical Structure Chemical Name
Bensulide  S-(O,O-diisopropyl phosphorodithioate) ester of N-(2-mercaptoethyl)benzenesulfonamide	**Bensulide oxygen analog**  S-(O,O-diisopropyl phosphorothioate) ester of N-(2-mercaptoethyl)benzenesulfonamide

iii. GLN 860.1300: Nature of the Residue - Livestock

Data pertaining to the nature of the residue in animals are not required. The only livestock feed item associated with registered bensulide uses is carrot culls, and product labels currently bear a restriction against the feeding of treated carrots to livestock. Although the Agency normally does not support this type of feeding restriction, HED has allowed this restriction because use of bensulide on carrots is limited to TX and low residues are present on carrots. HED reserves the right to require livestock metabolism studies if the registrant requests registration of additional uses of bensulide.

iv. GLN 860.1340: Residue Analytical Methods

Adequate methods are available for data collection and tolerance enforcement for plant commodities. The Pesticide Analytical Manual (PAM) Vol. II lists a gas-liquid chromatographic (GC) method (Method I), using either phosphorus-sensitive thermionic detection or flame photometric detection, for the determination of bensulide and bensulide oxygen analog in plant commodities. A thin-layer chromatographic (TLC) method (Method A) is available for confirmation. Method I uses benzene as a solvent. Methods used for data collection were modifications of Method I with the substitution of toluene for benzene.

HED had previously reserved the requirement for independent laboratory validation of a new enforcement method [high-pressure liquid chromatographic (HPLC) method] pending determination of bensulide residues of concern. Because HED determined that bensulide residues of concern are those that are currently regulated, no new enforcement method, and therefore no independent laboratory validation, is required.

v. GLN 860.1360: Multiresidue Methods

The 2/97 FDA PESTDATA database (PAM Volume I, Appendix I) indicates that bensulide is completely recovered (>80%) using Multiresidue Methods Sections 302 (Luke Method; Protocol D) and 304 (Mills Method; Protocol E, fatty foods) and partially recovered (70%) using Section 303 (Mills, Onley, Gaither Method; Protocol E, non-fatty foods). No information regarding the recovery of bensulide oxygen analog using Multiresidue Methods is included in the PESTDATA database.

vi. GLN 860.1380: Storage Stability Data

The final results of an ongoing 3-year storage stability study have been submitted. The reregistration requirements for storage stability data are fulfilled for the following commodities with existing tolerances for bensulide: carrots, onions (dry bulb), cucurbits, leafy vegetables, and bell peppers. Data are also available to support tolerances proposed for Brassica (cole) leafy vegetables. There are no currently registered uses of bensulide on cotton; therefore the tolerances should be revoked, and storage stability data to support the tolerance are not required.

The final storage stability data indicate some degree of instability of residues of bensulide *per se* in/on selected raw agricultural commodities (RACs) under frozen storage conditions. Residues of bensulide *per se* were demonstrated to be stable for up to 6 months in/on cabbage and cucumber, and for less than 3 months in/on broccoli and leaf lettuce. Residues of bensulide *per se* declined by 55-61% in/on broccoli after 12 months and by 51-53% in cabbage, 43-46% in/on cucumber, and 57-59% in/on leaf lettuce after 36 months.

Based on previously submitted storage stability data reviewed under Phase IV, bensulide *per se* has been demonstrated to be stable for a period of three years in alfalfa, almonds, apples, corn, oranges, peppers, potatoes, soybeans, and wheat. Storage stability data from potatoes have been translated to cover carrots. Similarly, storage stability data from peppers have been translated to cover tomatoes.

Residues of bensulide oxygen analog are relatively stable in/on broccoli and onions for up to 12 months, and in/on cabbage, carrots, cucumbers, lettuce (leaf), and bell peppers for up to 36 months.

The storage conditions and intervals of the field trial samples for representative commodities have been submitted. HED has taken into consideration the results of the available storage stability data during the conduct of tolerance reassessment.

vii. GLN 860.1500: Crop Field Trials

The reregistration requirements for magnitude of the residue in/on all raw agricultural commodities (RACs) except non-bell peppers have been fulfilled. The registrant must either restrict use to bell peppers or perform three geographically representative field trials on non-bell peppers. Adequate field trial data depicting bensulide residues of concern following treatments according to the maximum registered use patterns have been submitted for all RACs. Refer to the "Tolerance Reassessment Summary" for recommendations regarding appropriate tolerance levels. Label revisions are required for some crops in order to reflect current Agency policies and/or to reflect the parameters of use patterns for which field trial data are available; see "GLN 860.1200: Directions for Use."

Although Gowan currently has no registered uses of bensulide on tomatoes, the registrant had previously proposed to retain the tomato tolerance for import purposes. In order to determine whether the established tolerance is adequate to cover bensulide residues of concern in/on imported tomatoes, the registrant must submit copies of product labels with English translations from all countries from which bensulide-treated tomatoes may be imported into the U.S. In addition, twelve tomato crop field trials must be conducted in Mexico to support a tolerance with no U.S. registrations, i.e., use on imported tomatoes. If the registrant wishes to register domestic use of bensulide on tomatoes, the available field trial data would support a use pattern identical to the registered use pattern on peppers.

No additional field trial data are required for cotton because there are currently no registered uses of bensulide on this crop. In addition, no field trial data are required to support use of bensulide on grass grown for seed because this use has been deleted from product labels.

viii. GLN 860.1520: Processed Food/Feed

The reregistration requirements for magnitude of the residue in the processed commodities of imported tomatoes have not been fulfilled; a tomato processing study must be submitted. No additional data are required for cottonseed processed commodities because there are currently no registered uses of bensulide on cotton.

ix. GLN 860.1480: Meat, Milk, Poultry, Eggs

Data pertaining to the magnitude of the residue in meat, milk, poultry, and eggs are not required. The only livestock feed item associated with registered bensulide uses is carrot culls, and product labels currently bear a restriction against the feeding of treated carrots to livestock. Although the Agency normally does not support this type of feeding restriction, because use of bensulide on carrots is limited to TX (produces about 4% of the U.S. carrot crop) and low residues are present on carrots, HED has allowed this restriction. HED reserves the right to require livestock feeding studies if the registrant requests registration of additional uses of bensulide.

x. GLN 860.1400: Water, Fish, and Irrigated Crops

Bensulide is presently not registered for direct use on water and aquatic food and feed crops; therefore, no residue chemistry data are required under this guideline topic.

xi. GLN 860.1460: Food Handling

Bensulide is presently not registered for use in food-handling establishments; therefore, no residue chemistry data are required under this guideline topic.

xii. GLNs 860.1850 and 860.1900: Confined/Field Accumulation in Rotational Crops

The reregistration requirements for accumulation in rotational crops are fulfilled. An adequate confined rotational crop study has been submitted and evaluated. HED concluded that no limited field trials or rotational crop tolerances would be required, provided that a 120-day plantback interval is established for rotational crops. Limited field rotational crop trials would be required to support plantback intervals of less than 120 days. Currently, all product labels bear a plantback interval of 120 days for all crops not included on the label.

xiii. TOLERANCE REASSESSMENT SUMMARY

Tolerances for residues of bensulide in/on plant commodities [40 CFR §180.241] are presently

expressed in terms of the combined residues of bensulide and its oxygen analog. Following evaluation of plant metabolism studies, HED has determined that the bensulide residues that warrant regulation in plant commodities are those which are currently regulated. HED notes that the chemical name for the bensulide oxygen analog in the entry under 40CFR §180.241 is incorrect. The correct name [S-(O,O-diisopropyl phosphorothioate) ester of *N*-(2-mercaptoethyl)benzenesulfonamide] should be entered.

A summary of bensulide tolerance reassessments is presented in Table 5.

Tolerances Listed Under 40 CFR §180.241:

Adequate data are available to reassess the established tolerances for the following commodities, **as defined**: cucurbits, carrots, bell peppers, leafy vegetables, and onions (dry bulb). The phrase "negligible residues" should be removed from bensulide tolerance definitions. HED recommends that tolerances for the following commodities: curcurbits, and leafy vegetables be revised from 0.1 ppm to 0.15 ppm to account for the instability of bensulide per se in/on these commodities as evidenced in a nonconcurrent storage stability study. This recommendation was agreed upon by HED's Chemistry Science Advisory Council at a meeting held on September 8, 1997.

Based on the storage intervals for various crops and the stability data submitted, HED believes that residues of bensulide oxon were stable during the given storage periods prior to analysis. Based on these same data, HED has determined that residues of bensulide *per se* are unstable in a variety of crops. In general, an approximate loss of 50% of the initial residues of bensulide *per se* could be expected across a variety of crops.

The Agency has taken into consideration the results of the available storage stability data during tolerance reassessment, and concluded that in order to account for potential residue losses during storage prior to analysis, the tolerance for bensulide residues should be increased from 0.10 ppm [based on non-detectable levels of bensulide *per se* (0.05 ppm) plus bensulide oxon (0.05 ppm)] to 0.15 ppm (based on twice the limit of detection for bensulide *per se* (0.10 ppm) plus the limit of detection for bensulide oxon (0.05 ppm)) for the following commodities or crop groups: curcurbits, leafy vegetables, Brassica (Cole) leafy vegetables group.

Residues of bensulide and bensulide oxon were stable in carrots (data translated from potatoes), onions, and bell peppers during the periods of storage prior to analysis. Therefore, tolerances for these commodities are based on field trial data that has not been corrected for residue losses during storage.

Note that the tolerance for onions (dry bulb) will cover uses on garlic and shallots. In addition, the established tolerance for carrots must be revised to a tolerance with regional registration.

The established tolerance for cottonseed should be revoked because there are currently no registered uses of bensulide on cotton.

Tolerances To Be Proposed Under 40 CFR §180.241:

A tolerance must be proposed for the Brassica (cole) vegetables group. An appropriate level for this tolerance has been determined that reflects storage stability considerations. The Agency recommends the registrant propose a tolerance of 0.15 ppm.

Table 5: Tolerance Reassessment Summary for Bensulide.

Commodity	Current Tolerance, ppm	Tolerance Reassessment, ppm[1]	Comment/ *[Correct Commodity Definition]*
Tolerances Listed Under 40 CFR §180.241			
Carrots	0.1	0.10	This tolerance must be modified to one with regional registration (TX).
Cottonseed	0.1	Revoke	There are currently no registered uses of bensulide on cotton.
Cucurbits	0.1	0.15	*[Cucurbit Vegetables Group]*
Fruiting Vegetables	0.1	0.10	*[Fruiting Vegetables (except cucurbits) Group]*
Leafy vegetables	0.1	0.15	*[Leafy Vegetables (except Brassica Vegetables) Group]*
Onions (dry bulb)	0.1	0.10	
Tolerances to be Proposed			
Brassica (Cole) Leafy Vegetables Group	--	0.15[2]	*[Brassica (Cole) Leafy Vegetables]*

[1] Existing tolerances have been reassessed in light of the submitted 3-year storage stability study for bensulide and bensulide oxon.

[2] The registrant should propose a tolerance of 0.15 ppm for Brassica (Cole) Leafy Vegetables.

xiv. CODEX HARMONIZATION

There are no Codex Maximum Residue Limits (MRLs) established for bensulide. Therefore, there are no issues of compatibility between U.S. tolerances and Codex MRLs.

3.b. Dietary Risk Assessment and Characterization

i. Chronic Risk (Theoretical Maximum Residue Contribution, TMRC)

A chronic dietary assessment is performed to estimate the lifetime risk of consuming an average amount of bensulide residues. The assessment uses 3-day average consumption values from USDA's 1977-1978 Nationwide Food Consumption Survey and the reassessed tolerance level residues. The Reference Dose (RfD) used in the analysis for chronic risk is 0.005 mg/kg bwt/day, based on a NOEL of 0.5 mg/kg/day from a one-year feeding study in dogs with an uncertainty factor of 100. At the next highest dose level (4 mg/kg/day), significant inhibition of plasma cholinesterase activity in both sexes and brain cholinesterase activity in males was obeserved (See HazID Committee Report, 7/31/97). The residue levels used in the TMRC analyses are the reassessed tolerance levels presented in Table 5.

A DRES (Dietary Risk Evaluation System) chronic exposure analysis was performed using tolerance level residues and 100 percent crop treated information to estimate the Theoretical Maximum Residue Contribution (TMRC) for the general population and 22 subgroups.

Using the reassessed tolerance levels for cucurbits, fruiting vegetables except peppers, and leafy vegetables and deleting the use on cottonseed result in a TMRC which represents 7.5% of the RfD for the U.S. general population. The highest subgroup, Children (1-6 years old) represents 12.5% of the RfD.

The DRES analysis for bensulide can be considered to be an over-estimate of dietary exposure, since all residues were assumed at tolerance levels and 100 percent of the commodities were assumed to be treated with bensulide. The chronic dietary risk from all uses recommended through reregistration is not of concern.

ii. Carcinogenic Risk (TMRC)

Bensulide is classified as a Group E chemical, indicating evidence of non-carcinogenicity for humans.(See HazID Committee Report, 7/31/97).

iii. Acute Dietary Risk (TMRC)

The NOEL for estimating acute dietary risk is 15 mg/kg bwt/day from an acute neurotoxicity study in the rat and is based on 80% inhibition of plasma cholinesterase activity in females on Day 0 observed at 50 mg/kg/day (See HazID Committee Report, 7/31/97).

The Margin of Exposure (MOE) for acute dietary risk is a measure of how close the high end exposure comes to the NOEL (the highest dose at which no effects were observed in the laboratory test), and is calculated as the ratio of the NOEL to the exposure (NOEL/exposure = MOE). Generally, acute dietary margins of exposure greater than 100 tend to cause no dietary concern when the NOEL is taken from an animal study.

Use of the reassessed tolerances presented in Table 5 results in the following MOEs:

U.S. General Population = 3751
Infants (<1 year) = 1500
Children (1 to 6 years) = 1500

These MOEs do not exceed the HED's level of concern regarding acute dietary exposure for all uses recommended through reregistration.

4. OCCUPATIONAL AND RESIDENTIAL EXPOSURE/RISK ASSESSMENT AND CHARACTERIZATION

4.a. Occupational and Residential Exposure

An occupational and/or residential exposure assessment is required for an active ingredient if (1) certain toxicological criteria are triggered and (2) there is potential exposure to handlers (mixers, loaders, applicators, etc.) during use or to persons entering treated sites after application is complete.

i. Summary of Use Patterns and Formulations - Occupational and Residential

Bensulide, S-(0,0-Diisopropyl phosphorodithioate) ester of N-(2-mercaptoethyl) benzenesulfonamide, is a selective organophosphate herbicide registered for a variety of terrestrial food crop, terrestrial non-food crop, and outdoor residential uses (classifications are based on LUIS report categories). Bensulide is formulated as a technical-grade manufacturing product (92 percent active ingredient), three emulsifiable concentrate formulations (two at 4 and one at 6 pounds active ingredient per gallon), and as several granular formulations (3.6, 5.25, 7.0, 8.5, and 12.5 percent active ingredient). Emulsifiable concentrate (EC) products are labeled for use in all markets while granular products are labeled for use in only the terrestrial non-food and outdoor residential markets. The only product labelled for homeowner use is the 3.6G (Reg. No. 869-212).

Bensulide is applied as a pre-plant or pre-emergent herbicide in agricultural settings (i.e., to food crops) while non-food/outdoor residential applications (i.e., to turf and ornamentals) are made to established areas (e.g., lawns or golf course greens) prior to the emergence of the target plant species. "The herbicidal activity of bensulide is highly dependent on watering the material into the soil soon after application, so it is used almost entirely on irrigated crops and on turf into which it can be watered." Additionally, when applied pre-plant in agricultural settings, bensulide is generally soil incorporated. Bensulide can be applied by the use of chemigation, groundboom sprayers, handheld sprayers (low and high pressure devices and low pressure/high volume sprayguns commonly used on turf), backpack sprayers, tractor-drawn granular spreaders, push-type granular lawn spreaders, and bellygrinders. Aerial application is not precluded specifically on any bensulide label but correspondence from the registrant indicates that all agricultural applications of bensulide, the only scenario for which aerial applications seem appropriate, are completed only using ground equipment. Hence, exposures and risks associated with aerial application are not addressed in this document. Additionally, according to the registrant, greenhouse and outdoor uses "in commercial nurseries" are "negligible or nonexistent" even though labelling does not preclude these use patterns. Sod farm uses are also not apparently included on any label and are actually excluded by EPA Reg. No. 538-26. The aerial, greenhouse use, and sod farm scenarios should be addressed during label development to ensure that these use scenarios are not permitted without a further assessment. Bulk packaging is also used commercially for bensulide, particularly, in the desert southwest and the Rio Grande valley; however, because no data exist for bulk packaging, all mixer/loader assessments are based on more typical packaging.

Bensulide use sites are terrestrial food crops (60-65% of all use), terrestrial non-food crops

(primarily golf course greens, 25-30% of all use), and residential outdoor use (approximately 7% of all use)." Application rates vary from 3 to 12.5 pounds active ingredient per acre depending upon the application scenario. According to the registrants, "virtually all agricultural uses involve the 4EC formulation" (the 6EC product is relatively new and its overall use is negligible). Additionally, "professional applications on golf course greens and other turf areas ... are generally made with the 4EC formulation, although 12.5%, 8.5%, 7%, and 5.25% granules are also used." The EC formulations account for 85 percent of the bensulide formulated ("both agricultural and turf use") while approximately "8 percent is formulated as granular products for professional use, and approximately 7 percent of the total active ingredient is formulated as a 3.6 percent granule for homeowner use."

As indicated above, bensulide can be applied to terrestrial food crops, terrestrial non-food crops, and in outdoor residential settings. Leafy vegetables, dry bulb vegetables, cucurbits, cole crops, peppers, and carrots account for the majority of the agricultural uses (63.7 percent of all bensulide used). Use on golf greens accounts for another 27.3 percent of the total bensulide used while professionally-treated lawns and lawns treated by homeowners account for another 1.8 and 7.3 percent of the bensulide used, respectively.

Specifically, based on available labeling, bensulide can potentially be used to treat the following crops/targets (examples of each group/type are presented below):

Terrestrial Food Crops Include:

Curcurbit Vegetable Group: Chinese waxgourd, citron melon, cucumbers, gherkin, gourds, cucuzzi, chinese okra, melons (including muskmelon, true cantaloupe, cantaloupe, casaba, crenshaw melon, golden pershaw melon, honeydew melon, mango melon, persian melon, pineapple melon, santa claus melon, snake melon), pumpkins, summer squash, winter squash, and watermelons.

Leafy and Stem Vegetable Group: amranth, broccoli, chinese broccoli, raab broccoli, brussel sprouts, cabbage, chinese cabbage, cardoon, cauliflower, collards, kale, kohlrabi, mustard greens, mustard spinach, rape greens, celery, chinese celery, celtuce, chervil, chrysanthemum, corn salad, cress, dandelion, dock, endive, Florida fennel, lettuce, orach, parsley, radicchio, and swiss chard.

Fruiting Vegetables: Eggplant, ground cherry, pepinos, peppers (bell peppers, chili peppers, cooking peppers, pimentos, sweet peppers), and tomatillo.

Root Crop Vegetables: Carrots, chayote, garlic, onion, and shallots.

Terrestrial Non-Food Crops and Outdoor Residential Targets Include:

Established Turfgrasses: bahiagrass, bentgrass, Bermudagrass, perennial bluegrass, centipede, fescue, pensacola bahia, perennial ryegrass, poa trivialis, St. Augustine grass, red top, and

zoysia grass.

Bulbs: daffodil, dahlia, freesia, gladiolus, narcissus, ranunculus, and tulip.

Deciduous Trees, Shrubs, and Evergreens: abelia, azaelea, azara, boxwood, daphne, holly, juniper, monterey cypress, monterey pine, myrtle, privet, pyracantha, sandankwa, tobira, and xylosma.

Ground Covers: ajuga, calendula, hypericum, ice plant, ivy, pachysandra, periwinkle, sedum, and wild strawberry.

Herbaceous Plants: alyssum, aster, bachelor's button, calendula, candy-tuft, coral bell, daisy, marigold, pansy, primrose, stock, sweet pea, and wallflower.

Occupational-Use and Homeowner-Use Products

At this time, products containing bensulide are intended for occupational and homeowner uses. Only the 3.6G product (Reg. No. 869-212) is specifically labeled for homeowner use. Several other products can be used occupationally (by professional applicators) in the residential market (i.e., granulars and an EC formulation) and in the agricultural market.

ii. Handler Exposure Scenarios & Assumptions

EPA has determined that handlers are likely to be exposed during bensulide use (mixers, loaders, and applicators). The anticipated use patterns and current labeling indicate several major exposure scenarios based on the types of equipment that potentially can be used to make bensulide applications. These scenarios include: (1a) mixing/loading liquids for chemigation application; (1b) mixing/loading liquids for groundboom application; (1c) mixing/loading liquids for professional turf applications (2) loading granulars for tractor-drawn spreader application (3) applying sprays with a groundboom sprayer; (4) applying granulars with a tractor-drawn spreader; (5) mixing/loading/applying with a low pressure handwand; (6) mixing/loading/applying with a high pressure handwand; (7) mixing/loading/applying with a backpack sprayer; (8) mixing/loading/applying with a low pressure/high volume handgun (turf grass application); (9) loading/applying with a push-type granular lawn spreader; and (10) loading/applying with a bellygrinder.

The following assumptions and factors were used in order to complete this exposure assessment:

- Average body weight of a female handler is 60 kg. This body weight is used in the short-term assessment, since the endpoint of concern is based on a maternal effect.

- Average body weight of an adult handler is 70 kg. This body weight is used in the intermediate-term assessment, since the endpoint of concern is not sex- specific (i.e., the cholinesterase inhibition could be assumed to occur in males or females).

- Average work day interval represents an 8 hour workday (e.g., the acres treated or volume of spray solution prepared in a typical day).

- Daily areas and volumes (as appropriate) to be treated in each scenario include: 50 acres during mixing/loading for professional turf applications (10 trucks/day x 5 acres/truck); 350 acres for chemigation applications; 80 acres for groundboom applications in an agricultural setting and 40 acres in non-food settings (i.e., golf course turf); 40 acres for granular tractor-drawn spreaders (i.e., golf course turf); 0.5 acre (homeowners) and 5 acres (occupational) for push-type granular spreader and bellygrinder applications; 5 acre (occupational only) for backpack, low-pressure handwand, low pressure/high volume handguns used to treat turfgrass; and 1000 gallons for high-pressure handwand for turfgrass. These values are believed to represent typical to reasonable high-end estimates of daily area treated.

- Calculations are completed at the minimum and maximum application rates recommended by the available bensulide labels to bracket risk levels associated with the various use patterns. No use data were provided by the registrant concerning the actual application rates that are commonly used for bensulide.

- Due to a lack of scenario-specific data, HED is often forced to calculate unit exposure values using generic protection factors that are applied to represent various risk mitigation options (i.e., the use of PPE or Personal Protective Equipment and engineering controls). PPE protection factors include those representing layers of clothing (50%), chemical-resistant gloves (90%), and respiratory protection (80 to 95% depending upon mitigation selected). Engineering controls are generally assigned a protection factor of 90 percent. Engineering controls may include closed mixing/loading systems, closed cabs/cockpits, and "Lock-n-Load" type systems for granulars.

- Generally, the use of PPE (Personal Protective Equipment) and engineering controls are not considered acceptable options for products sold for use by homeowners because they are generally not available and/or are inappropriate for the exposure scenario (e.g., acceptability rationale is based on a lack of enforcement, available PPE, and training).

iii. Handler Exposure Assessment

No chemical-specific handler exposure data were submitted in support of the reregistration of bensulide. Therefore, an exposure assessment for each use scenario was developed, where appropriate data are available, using surrogate values calculated using the *Pesticide Handlers Exposure Database (PHED) Version 1.1.* PHED was designed by a task force consisting of

representatives from the U.S. EPA, Health Canada, the California Department of Pesticide Regulation, and member companies of the American Crop Protection Association. PHED is a generic database containing measured exposure data for workers involved in the handling or application of pesticides in the field (i.e., currently contains data for over 2000 monitored exposure events). The basic assumption underlying the system is that exposure to pesticide handlers can be calculated using the monitored data as exposure is primarily a function of the physical parameters of handling and application process (e.g., packaging type, application method, and clothing scenario). PHED also contains algorithms that allow the user to complete surrogate task-based exposure assessments beginning with one of the four main data files contained in the system (i.e., mixer/loader, applicator, flagger, and mixer/loader/applicator).

Users can select data from each major PHED file and construct exposure scenarios that are representative of the use of the chemical. However, to add consistency to the risk assessment process, the EPA in conjunction with the PHED task force has evaluated all data within the system and developed a surrogate exposure table that contains a series of standard unit exposure values for various exposure scenarios. These standard unit exposure values are the basis for this assessment. The standard exposure values (i.e., the unit exposure values included in the exposure and risk assessment tables) are based on the "best fit" values calculated by PHED. PHED calculates "best fit" exposure values by assessing the distributions of exposures for each body part included in datasets selected for the assessment (e.g., chest or forearm) and then calculating a composite exposure value representing the entire body. PHED categorizes distributions as normal, lognormal, or in an "other" category. Generally, most data contained in PHED are lognormally distributed or fall into the PHED "other" distribution category. If the distribution is lognormal, the geometric mean for the distribution is used in the calculation of the "best fit" exposure value. If the data are an "other" distribution, the median value of the dataset is used in the calculation of the "best fit" exposure value. As a result, the surrogate unit exposure values that serve as the basis for this assessment generally range from the geometric mean to the median of the selected dataset.

Handler exposure assessments are completed by the EPA using a baseline exposure scenario and, if required, increasing levels of risk mitigation (PPE and engineering controls) to achieve an appropriate margin of exposure or cancer risk. The baseline scenario generally represents a handler wearing long pants, a long-sleeved shirt, and no chemical-resistant gloves (there are exceptions pertaining to the use of gloves and these are noted). The calculation of baseline exposures (mg/day) are presented in Table 6. These daily exposures are used to complete the dermal risk assessment for the short-term exposure scenario (Table 7) and the dermal risk assessment for the intermediate-term exposure scenario (Table 8). Tables 8 and 9 also include exposure/risk calculations for increasing levels of PPE and engineering controls as required for each exposure scenario. Table 9 presents the inhalation risk calculations. The equations used to calculate Margin of Exposure (MOE) values presented in Tables 8, 9, and 10 are included in Section 4.b. of this document, as these equations are pertinent to the risk evaluation and not the exposure process. Table 10 summarizes the caveats and parameters specific to the surrogate data used for each exposure scenario and corresponding exposure/risk assessment. These caveats include the source of the data and an assessment of the overall quality of the data. The assessment of data quality is based on the number of observations and the available quality control data. The quality control data are assessed based on a grading criteria established by the PHED task force.

The calculations of daily dermal exposure to bensulide by handlers are used to calculate the daily dose, and hence the risks, to those handlers. No chemical-specific dermal absorption data are available. Therefore, a dermal absorption value of 20 percent that has been estimated based on the ratio of the acute dermal and acute oral endpoints is used in all calculations. Potential daily dermal exposure is calculated using the following formula:

Daily dermal exposure (mg ai/day) =

Unit exposure (mg ai/lb ai) x Appl. Rate (lb ai/A) x Daily Acres Treated (A/day).

[Note: When the high pressure handwand device is used, (lb ai/acre) and (A/day) are replaced, respectively, with (lb ai/gal) and (gal/day).]

The calculations of daily inhalation exposure to bensulide by handlers are used to calculate the daily dose, and hence the risks, to those handlers. Daily inhalation exposure levels were calculated for inclusion into the PHED surrogate exposure tables and presented as (μg/lb ai) based on a human inhalation rate of 29 L/minute and an 8 hour working day. However, the risk calculations presented in this document are based on a direct comparison of the concentration-based inhalation endpoint and a surrogate Time-Weighted Average (TWA) concentration associated with a particular exposure scenario (mg/L/lb ai). The TWA value is calculated as follows:

Average Air Concentration (mg/L)=

$$\frac{\text{Unit exposure (µg ai/lb ai) x Appl. Rate (lb ai/A) x Daily Acres Treated (A/day)}}{13.92\ m^3\text{/day x } 1000\text{µg/mg x } 1000\ L/m^3}$$

[Note: The daily inhalation rate of 13.92 m^3/day is based on the following calculation. (29 L/min x 60 min/hr x 8 hr/day)/(1 m^3/ 1000 L). When the high pressure handwand device is used, (lb ai/acre) and (A/day) are replaced, respectively, with (lb ai/gal) and (gal/day).]

Table 6: Baseline Exposures to Bensulide

Exposure Scenario (Scen.#)	Baseline Dermal Unit Exposure (mg/lb ai)[a]	Baseline Inhalation Unit Exposure (µg/lb ai)[b]	Range of Application Rates (lb ai/acre)[c]	Crop Type Or Target[d]	Daily Acres Treated[e]	Daily Dermal Exposure (mg/day)[f]	Daily Inhalation Exposure (mg/day)[g]
Mixer/Loader Exposure							
Mixing/Loading Liquids for Chemigation Application (1a)	2.9	1.2	3	Ag	350	3,045	1.3
			6			6,090	2.5
Mixing/Loading Liquids for Groundboom Application (1b)			3	Ag	80	696	0.3
			6			1,392	0.6
			7.5	Turf & Ornamentals	40	870	0.4
			12.5			1,450	0.6
Mixing/Loading Liquids for Professional Applications To Turf Using a Low Pressure/High Volume Handgun (1c)			7.5	Turf & Ornamentals	50	1,088	0.5
			12.5			1,813	0.8
Loading Granulars for Tractor-Drawn Spreader Application (2)	0.0076	1.7	7.5	Turf & Ornamentals	40	2	0.5
			12.5			4	0.9
Applicator Exposure							
Applying Sprays with a Groundboom Sprayer (3)	0.015	0.7	3	Ag	80	4	0.2
			6			7	0.3
			7.5	Turf & Ornamentals	40	5	0.2
			12.5			8	0.4
Applying Granulars with a Tractor-Drawn Spreader (4)	0.01	1.2	7.5	Turf & Ornamentals	40	3	0.4
			12.5			5	0.6

Table 6: Baseline Exposures to Bensulide

Exposure Scenario (Scen.#)	Baseline Dermal Unit Exposure (mg/lb ai)[a]	Baseline Inhalation Unit Exposure (µg/lb ai)[b]	Range of Application Rates (lb ai/acre)[c]	Crop Type Or Target[d]	Daily Acres Treated[e]	Daily Dermal Exposure (mg/day)[f]	Daily Inhalation Exposure (mg/day)[g]
Mixer/Loader/Applicator Exposure							
Mixing/Loading/Applying with a Low Pressure Handwand (5)	103.8	31.2	7.5	Turf & Ornamentals	5 (O)	3,893	1.2
			12.5		5 (O)	6,488	2.0
Mixing/Loading/Applying with a High Pressure Handwand (6)	2.5 (gloves)	117	0.16 lb ai/gal	Turf & Ornamentals	1,000 gallons	400	18.7
Mixing/Loading/Applying with a Backpack Sprayer (7)	2.5 (gloves)	30.2	7.5	Turf & Ornamentals	5 (O)	94	1.1
			12.5		5 (O)	156	1.9
Mixing/Loading/Applying with a Low Pressure/High Volume Handgun (turf grass application) (8)	3.7	2.6	7.5	Turf & Ornamentals	5 (O)	139	0.1
			12.5		5 (O)	231	0.2
Mixing/Loading/Applying with a Push-Type Granular Spreader (9)	2.9	6.3	7.5	Turf & Ornamentals	0.5 (H)	11	0.02
					5 (O)	109	0.2
			12.5		0.5 (H)	18	0.04
					5 (O)	181	0.4

Table 6: Baseline Exposures to Bensulide

Exposure Scenario (Scen.#)	Baseline Dermal Unit Exposure (mg/lb ai)[a]	Baseline Inhalation Unit Exposure (µg/lb ai)[b]	Range of Application Rates (lb ai/acre)[c]	Crop Type Or Target[d]	Daily Acres Treated[e]	Daily Dermal Exposure (mg/day)[f]	Daily Inhalation Exposure (mg/day)[g]
Mixing/Loading/Applying with a Bellygrinder (10)	10.4	61.8	7.5	Turf & Ornamentals	0.5 (H)	39	0.2
					5 (O)	390	2.3
			12.5		0.5 (H)	65	0.4
					5 (O)	650	3.9

a Baseline dermal unit exposures represent long pants, long sleeved shirt, no gloves, open mixing/loading, and open cab tractors as appropriate. The only exceptions are for exposure scenarios 6 (Mixing/Loading/Applying with a High Pressure Handwand) & 7 (Mixing/Loading/Applying with a Backpack Sprayer) where the PHED unit exposure value includes the use of protective gloves (i.e., it is not appropriate to calculate non-gloved exposures based on values at the LOQ which is the case for these scenarios). In some cases, appropriate protection factors were applied to calculate baseline exposures based on available data (see *Exposure Scenario Descriptions Table* for further information).

b Baseline inhalation unit exposures reflect no respiratory protection.

c Application rates represent the minimum and maximum values found in the bensulide labels for each crop/target type. According to bensulide labels, the minimum and maximum seasonal rates for food crops and non-food/turf/ornamentals are (each are presented for exposure/risk assessment purposes):
Food Crops (i.e., typical agriculture)
minimum: 3 lb ai/acre (e.g., garlic, bulb onions, shallots) which is available in emulsifiable liquid (e.g., EPA Reg. 10163-222)
maximum: 6 lb ai/acre (e.g.,cucumber, squash, melons, etc.) which is available in emulsifiable liquid (e.g., EPA Regs .10163-222, 10163-200, 2217-696)
Non-Food Crops & Turf/Ornamentals (i.e., turf & ornamentals)
minimum: 7.5 lb ai/acre for granules (EPA Reg. 10163-204-33955) and as an emulsifiable concentrate (EPA Reg. 2217-696)
maximum: 12.5 lb ai/acre for an emulsifiable concentrate (EPA Reg. 34704-211) and granules (EPA Regs 2217-696, 10163-196-2217, 10163-204-33955, 34704-209)

d Crop Type or Target provides a general description of the intended uses of various products containing bensulide. Separate categories are presented because of the distinct differences in application rates and acres treated. *Ag* = agricultural crops and *Turf & Ornamentals* = any non-food target including turf and ornamentals.

e Daily acres treated or gallons used values are from the EPA estimates of acreage that could be treated in a single day for each exposure scenario of concern based on the application method. (H) = Homeowner uses and (O) = Occupational uses.

f Daily Dermal Exposure (mg/day) = Exposure (mg/lb ai) x Application Rate (lb ai/acre) x Acres Treated/Day
[Note: Application Rate and Acres Treated/Day are replaced by Concentration (lb ai/gal) and Gallons Used/Day (gal/day) if the high pressure handwand is used.]

g Daily Inhalation Exposure (mg/day) = Exposure (µg/lb ai) x (1 mg/1000 µg) Conversion x Application Rate (lb ai/acre) x Acres Treated/Day
[Note: Application Rate and Acres Treated/Day are replaced by Concentration (lb ai/gal) and Gallons Used/Day (gal/day) if the high pressure handwand is used.]

Table 7: Short-Term Dermal Risks From Bensulide

Exposure Scenario (Scen #)	Crop Type or Target	Baseline Absorbed Dose (mg/kg/day)[a]	Baseline Dermal MOE[b]	Risk Mitigation Measures[c]					
				Additional PPE			Engineering Controls		
				PPE Unit Exp. (mg/lb ai)[d]	PPE Absorbed Dose (mg/kg/day)[a]	PPE MOE[b]	Eng. Controls Unit Exposure (mg/lb ai)[e]	Eng. Controls Absorbed Dose (mg/kg/day)[a]	Eng. Controls MOE[b]
Mixer/Loader Risk									
Mixing/Loading Liquids for Chemigation Application (1a)	Ag	10.2 min (O)	<1	0.025	0.088	63	0.009 (gloves)	0.032	170
		20.4 max (O)	<1		0.18	31		0.063	87
Mixing/Loading Liquids for Groundboom Application (1b)	Ag	2.4 min (O)	2		0.020	280		NA	NA
		4.6 max (O)	1		0.040	140		NA	NA
	Turf & Ornamentals	2.9 min (O)	2		0.025	220		NA	NA
		4.8 max (O)	1		0.042	130		NA	NA
Mixing/Loading Liquids for Professional Applications to Turf Using a Low Pressure/High Volume Handgun (1c)	Turf & Ornamentals	3.6 min (O)	2		0.031	180		NA	NA
		6.0 min (O)	<1		0.052	110		NA	NA
Mixing/Loading Granulars for Tractor-Drawn Spreader Application (2)	Turf & Ornamentals	0.007 min (O)	790	NA	NA	NA	NA	NA	NA
		0.013 max (O)	420		NA	NA			
Applicator Risk									
Applying Sprays with a Groundboom Sprayer (3)	Ag	0.013 min (O)	420	NA	NA	NA	NA	NA	NA
		0.023 max (O)	240		NA	NA		NA	NA
	Turf & Ornamentals	0.017 min (O)	320		NA	NA		NA	NA
		0.027 max (O)	200		NA	NA		NA	NA
Applying Granulars with a Tractor-Drawn Spreader (4)	Turf & Ornamentals	0.01 min (O)	550	NA	NA	NA	NA	NA	NA
		0.017 max (O)	320		NA	NA		NA	NA
Mixer/Loader/Applicator Risk									
Mixing/Loading/Applying with a Low Pressure Handwand (5)	Turf & Ornamentals	13 min (O)	<1	3.2	0.4	14	N/F	N/F	N/F
		21.6 max (O)	<1		0.7	8			
Mixing/Loading/Applying with a High Pressure Handwand (6)	Turf & Ornamentals	1.3 max (O)	4	1.3	0.7	8	N/F	N/F	N/F
Mixing/Loading/Applying with a Backpack Sprayer (7)	Turf & Ornamentals	0.31 min (O)	18	1.3	0.16	34	N/F	N/F	N/F
		0.52 max (O)	11		0.27	20			

Table 7: Short-Term Dermal Risks From Bensulide

Exposure Scenario (Scen #)	Crop Type or Target	Baseline Absorbed Dose (mg/kg/day)[a]	Baseline Dermal MOE[b]	Risk Mitigation Measures[c]					
				Additional PPE			Engineering Controls		
				PPE Unit Exp. (mg/lb ai)[d]	PPE Absorbed Dose (mg/kg/day)[a]	PPE MOE[b]	Eng. Controls Unit Exposure (mg/lb ai)[e]	Eng. Controls Absorbed Dose (mg/kg/day)[a]	Eng. Controls MOE[b]
Mixing/Loading/Applying with a Low Pressure/High Volume Handgun (turf grass application) (8)	Turf & Ornamentals	0.46 min (O)	12	0.2	0.025	220	N/F	N/F	N/F
		0.77 max (O)	7		0.042	130			
Mixing/Loading/Applying with a Push-Type Granular Spreader (9)	Turf & Ornamentals	0.037 min (H)	150	0.7	N/F	N/F	N/F	N/F	N/F
		0.36 min (O)	15		0.088	63			
		0.06 max (H)	92		N/F	N/F			
		0.6 max (O)	9		0.15	37			
Mixing/Loading/Applying with a Bellygrinder (10)	Turf & Ornamentals	0.13 min (H)	42	16.3	N/F	N/F	NF	NF	NF
		1.3 min (O)	4		2	3			
		0.22 max (H)	25		N/F	N/F			
		2.2 max (O)	3		3.4	2			

a Absorbed Dose (mg/kg/day) = (Daily Dermal Exposure (mg/day) x Dermal Absorption Factor (20%))/ Body weight (60 kg)
Daily Dermal Exposure excerpted from Table 1 and Dermal Absorption Factor for Bensulide is 20 percent. MOEs presented for minimum (min) and maximum (max) application rates in each scenario and, as appropriate, to delineate between homeowner (H) and occupational (O) scenarios.

b Short-Term Dermal MOE = (NOEL (5.5 mg/kg/day)/Absorbed Dermal Dose (mg/kg/day))

c N/F (Not Feasible) = The Agency does not consider personal protective equipment feasible for homeowner handlers or engineering controls an effective approach for mitigating exposures during the use of certain types of equipment.
N/A (Not Applicable) = Indicates the calculation is not required and no further mitigation is required as an MOE of 100 was already attained.

d Additional PPE:
1a/1b/1c: Double layer of clothing and chemical resistant gloves (50 % PF for clothing layer).
5: Double layer of clothing and chemical resistant gloves (50 % PF for clothing layer).
6: Double layer of clothing and chemical resistant gloves (50 % PF for clothing layer).
7: Double layer of clothing and chemical resistant gloves (50 % PF for clothing layer).
8: Double layer of clothing and chemical resistant gloves (50 % PF for clothing layer).
9: Double layer of clothing and chemical resistant gloves (50 % PF for clothing layer & 90 % PF for gloves).
10: Double layer of clothing and chemical resistant gloves (50 % PF for clothing layer).

e Engineering Controls:
1a: Closed mixing, single layer clothing, and chemical resistant gloves

Table 8: Intermediate-Term Dermal Risks to Bensulide

Exposure Scenario (Scen #)	Crop Type or Target	Baseline Absorbed Dose (mg/kg/day)[a]	Baseline Dermal MOE[b]	Risk Mitigation Measures[c]					
				Additional PPE			Engineering Controls		
				PPE Dermal Unit Exp. (mg/lb ai)[d]	PPE Absorbed Dose (mg/kg/day)[a]	PPE Dermal MOE[b]	Eng. Controls Dermal Unit Exposure (mg/lb ai)[e]	Eng. Controls Asorbed Dose (mg/kg/day)[a]	Eng. Controls Dermal MOE[b]
Mixer/Loader Risk									
Mixing/Loading Liquids for Chemigation Application (1a)	Ag	8.7 min (O)	<1	0.025	0.075	7	0.009 (gloves)	0.027	19
		17.4 max (O)	<1		0.15	3		0.054	9
Mixing/Loading Liquids for Groundboom Application (1b)	Ag	2.0 min (O)	<1		0.017	29		0.006	83
		4 .0 max (O)	<1		0.034	15		0.012	42
	Turf & Ornamentals	2.5 min (O)	<1		0.021	24		0.008	63
		4.1 max (O)	<1		0.036	14		0.013	38
Mixing/Loading Liquids for Professional Applications to Turf Using a Low Pressure/High Volume Handgun (1c)	Turf & Ornamentals	3.1 min (O)	<1		0.027	19		0.010	50
		5.2 min (O)	<1		0.045	11		0.016	31
Mixing/Loading Granulars for Tractor-Drawn Spreader Application (2)	Turf & Ornamentals	0.006 min (O)	83	0.0031	0.003	170	NA	NA	NA
		0.011 max (O)	45		0.004	130		NA	NA
Applicator Risk									
Applying Sprays with a Groundboom Sprayer (3)	Ag	0.011 min (O)	45	0.01	0.007	71	0.0067	0.005	100
		0.020 max (O)	25		0.014	36		0.009	56
	Turf & Ornamentals	0.014 min (O)	36		0.009	56		0.006	83
		0.023 max (O)	22		0.014	36		0.010	50

Table 8: Intermediate-Term Dermal Risks to Bensulide

Exposure Scenario (Scen #)	Crop Type or Target	Baseline Absorbed Dose (mg/kg/day)[a]	Baseline Dermal MOE[b]	Risk Mitigation Measures[c]					
				Additional PPE			Engineering Controls		
				PPE Dermal Unit Exp. (mg/lb ai)[d]	PPE Absorbed Dose (mg/kg/day)[a]	PPE Dermal MOE[b]	Eng. Controls Dermal Unit Exposure (mg/lb ai)[e]	Eng. Controls Asorbed Dose (mg/kg/day)[a]	Eng. Controls Dermal MOE[b]
Applying Granulars with a Tractor-Drawn Spreader (4)	Turf & Ornamentals	0.009 min (O)	56	0.004	0.003	170	0.002	NA	NA
		0.014 max (O)	36		0.006	83		0.003	170
Mixer/Loader/Applicator Risk									
Mixing/Loading/Applying with a Low Pressure Handwand (5)	Turf & Ornamentals	11.1 min (O)	<1	3.2	0.34	1	N/F	N/F	N/F
		18.5 max (O)	<1		0.57	<1			
Mixing/Loading/Applying with a High Pressure Handwand (6)	Turf & Ornamentals	1.11 max (O)	<1	1.3	0.60	<1	N/F	N/F	N/F
Mixing/Loading/Applying with a Backpack Sprayer (7)	Turf & Ornamentals	0.27 min (O)	2	1.3	0.14	4	N/F	N/F	N/F
		0.45 max (O)	1		0.23	2			
Mixing/Loading/Applying with a Low Pressure/High Volume Handgun (turf grass application) (8)	Turf & Ornamentals	0.40 min (O)	1	0.2	0.021	24	N/F	N/F	N/F
		0.66 max (O)	<1		0.036	14			
Mixing/Loading/Applying with a Push-Type Granular Spreader (9)	Turf & Ornamentals	0.031 min (H)	16	0.7	N/F	N/F	N/F	N/F	N/F
		0.31 min (O)	2		0.075	7			
		0.051 max (H)	10		N/F	N/F			
		0.52 max (O)	<1		0.13	4			
Mixing/Loading/Applying with a Bellygrinder (10)	Turf & Ornamentals	0.11 min (H)	5	16.3	N/F	N/F	NF	NF	NF
		1.11 min (O)	<1		1.7	<1			
		0.19 max (H)	3		N/F	N/F			
		1.9 max (O)	<1		2.9	<1			

a Daily Dermal Dose (mg/kg/day) = (Daily Dermal Exposure (mg/day) x Dermal Absorption Factor (20%))/ Body weight (70 kg)
Daily Dermal Exposure excerpted from Table 1 and Dermal Absorption Factor for Bensulide is 20 percent. MOEs presented for minimum (min) and maximum (max) application rates in each scenario and, as appropriate, to delineate between homeowner (H) and occupational (O) scenarios.

b Intermediate-Term Dermal MOE = (NOEL (0.5 mg/kg/day)/Daily Dermal Dose (mg/kg/day))

c N/F (Not Feasible) = The Agency does not consider personal protective equipment feasible for homeowner handlers or engineering controls an effective approach for mitigating exposures during the use of certain types of equipment. N/A (Not Applicable) = Indicates the calculation is not required and no further mitigation is required as an MOE of 100 was already attained.

d Additional PPE:

1a/1b/1c:	Double layer of clothing and chemical resistant gloves (50 % PF for clothing layer).
2:	Double layer of clothing and chemical resistant gloves (50 % PF for clothing layer).
3:	Double layer of clothing and chemical resistant gloves (50 % PF for clothing layer).
4:	Double layer of clothing and chemical resistant gloves (50 % PF for clothing layer & 90 % PF for gloves).
5:	Double layer of clothing and chemical resistant gloves (50 % PF for clothing layer).
6:	Double layer of clothing and chemical resistant gloves (50 % PF for clothing layer).
7:	Double layer of clothing and chemical resistant gloves (50 % PF for clothing layer).
8:	Double layer of clothing and chemical resistant gloves (50 % PF for clothing layer).
9:	Double layer of clothing and chemical resistant gloves (50 % PF for clothing layer & 90 % PF for gloves).
10:	Double layer of clothing and chemical resistant gloves (50 % PF for clothing layer).

e Engineering Controls:

1a/1b/1c:	Closed mixing, single layer clothing, and chemical resistant gloves.
3:	Closed cab, single layer of clothing, and no chemical resistant gloves.
4:	Closed cab, single layer of clothing, and no chemical resistant gloves.

Table 9: Inhalation Risks From Bensulide

Exposure Scenario (Scen #)	Crop Type or Target	Baseline Airborne Exposure TWA Concentration (mg/L)[a]	Baseline Inhalation MOE[b]	Risk Mitigation Measures[c]					
				Additional PPE			Engineering Controls		
				Unit Exposure[a] (mg/lb ai)	TWA Exposure Concentration[a] (mg/L)	MOE[b]	Unit Exposure[a] (mg/lb ai)	TWA Exposure Concentration[a] (mg/L)	MOE[b]
Mixer/Loader Risk									
Mixing/Loading Liquids for Chemigation Application (1a)	Ag	9.3e-5 min (O)	19,000	NA	NA	NA	NA	NA	NA
		1.8e-4 max (O)	9,700		NA	NA		NA	NA
Mixing/Loading Liquids for Groundboom Application (1b)	Ag	2.2e-5 min (O)	80,000		NA	NA		NA	NA
		4.3e-5 max (O)	41,000		NA	NA		NA	NA
	Turf & Ornamentals	2.9e-5 min (O)	60,000		NA	NA		NA	NA
		4.3e-5 max (O)	41,000		NA	NA		NA	NA
Mixing/Loading Liquids for Professional Applications to Turf Using a Low Pressure/High Volume Handgun (1c)	Turf & Ornamentals	3.6e-5 min (O)	49,000		NA	NA		NA	NA
		5.7e-5 min (O)	31,000		NA	NA		NA	NA
Mixing/Loading Granulars for Tractor-Drawn Spreader Application (2)	Turf & Ornamentals	3.6e-5 min (O)	49,000	NA	NA	NA	NA	NA	NA
		6.4e-5 max (O)	27,000		NA	NA			
Applicator Risk									
Applying Sprays with a Groundboom Sprayer (3)	Ag	1.4e-5 min (O)	130,000	NA	NA	NA	NA	NA	NA
		2.2e-5 max (O)	80,000		NA	NA		NA	NA
	Turf & Ornamentals	1.4e-5 min (O)	130,000		NA	NA		NA	NA
		2.9e-5 max (O)	60,000		NA	NA		NA	NA

Table 9: Inhalation Risks From Bensulide

Exposure Scenario (Scen #)	Crop Type or Target	Baseline Airborne Exposure TWA Concentration (mg/L)[a]	Baseline Inhalation MOE[b]	Risk Mitigation Measures[c]					
				Additional PPE			Engineering Controls		
				Unit Exposure[a] (mg/lb ai)	TWA Exposure Concentration[a] (mg/L)	MOE[b]	Unit Exposure[a] (mg/lb ai)	TWA Exposure Concentration[a] (mg/L)	MOE[b]
Applying Granulars with a Tractor-Drawn Spreader (4)	Turf & Ornamentals	2.9e-5 min (O)	60,000	NA	NA	NA	NA	NA	NA
		4.3e-5 max (O)	41,000		NA	NA		NA	NA
Mixer/Loader/Applicator Risk									
Mixing/Loading/Applying with a Low Pressure Handwand (5)	Turf & Ornamentals	8.6e-5 min (O)	20,000	NA	NA	NA	NA	NA	NA
		1.4e-4 max (O)	13,000		NA	NA			
Mixing/Loading/Applying with a High Pressure Handwand (6)	Turf & Ornamentals	1.3e-3 max (O)	1,300	NA	NA	NA	NA	NA	NA
Mixing/Loading/Applying with a Backpack Sprayer (7)	Turf & Ornamentals	7.9e-5 min (O)	22,000	NA	NA	NA	NA	NA	NA
		1.3e-4 max (O)	13,000		NA	NA			
Mixing/Loading/Applying with a Low Pressure/High Volume Handgun (turf grass application) (8)	Turf & Ornamentals	7.1e-6 min (O)	250,000	NA	NA	NA	NA	NA	NA
		1.4e-5 max (O)	130,000		NA	NA			
Mixing/Loading/Applying with a Push-Type Granular Spreader (9)	Turf & Ornamentals	1.4e-6 min (H)	1,300,000	NA	NA	NA	NA	NA	NA
		1.4e-5 min (O)	130,000		NA	NA			
		2.9e-6 max (H)	600,000		NA	NA			
		2.9e-5 max (O)	60,000		NA	NA			

Table 9: Inhalation Risks From Bensulide

Exposure Scenario (Scen #)	Crop Type or Target	Baseline Airborne Exposure TWA Concentration (mg/L)[a]	Baseline Inhalation MOE[b]	Risk Mitigation Measures[c]					
				Additional PPE			Engineering Controls		
				Unit Exposure[a] (mg/lb ai)	TWA Exposure Concentration[a] (mg/L)	MOE[b]	Unit Exposure[a] (mg/lb ai)	TWA Exposure Concentration[a] (mg/L)	MOE[b]
Mixing/Loading/Applying with a Bellygrinder (10)	Turf & Ornamentals	1.4e-5 min (H)	130,000	NA	NA	NA	NA	NA	NA
		1.7e-4 min (O)	10,000		NA	NA			
		2.9e-5 max (H)	60,000		NA	NA			
		2.8e-4 max (O)	6,000		NA	NA			

N/F (Not Feasible) = The Agency does not consider personal protective equipment feasible for homeowner handlers or engineering controls an effective approach for mitigating exposures during the use of certain types of equipment. NA (Not Applicable) = Indicates the calculation is not required and no further mitigation is required as an MOE of 100 was already achieved.

a The airborne exposure concentrations (i.e., Time-Weighted Average or TWA values) are calculated as follows:
[TWA] (mg/L) = (Inhalation Exposure (mg/day) x Inhalation Absorption Factor (%/100))/((13.92 m^3/day) x (1000μg/mg))
[Note: Inhalation Exposure calculations are explained further in Baseline Dermal and Inhalation Exposures Table. Inhalation Absorption is considered to be 100%.]

b Inhalation MOE calculated using a NOEL of 1.75 mg/L and the following formula:
MOE = (NOEL (1.75 mg/L)/TWA (mg/L))

Table 10: Exposure Scenario Descriptions for the Use of Bensulide

Exposure Scenario (Number)	Data Source	Standard Assumptions[a] (8-hr work day)	Comments[b]
Mixer/Loader Descriptors			
Mixing/Loading Liquid Formulations (1a/1b/1c)	PHED V1.1	350 acres for aerial, 80 acres for groundboom in agriculture, 40 acres for groundboom on golf course turf, and 10 professional applicators/day each treating 5 acres/day for the turf loading scenarios	**Baseline:** Hand, dermal, and inhalation are acceptable grades. Hand = 53 replicates; Dermal = 25 to 122 replicates; and Inhalation = 85 replicates. High confidence in hand/dermal and inhalation data. No protection factor was needed to define the unit exposure value. **PPE:** The same dermal data are used as for the baseline coupled with a 50% protection factor to account for an additional layer of clothing. Hand = acceptable grades. Hands = 59 replicates. High confidence in hand/dermal data. **Engineering Controls:** Hand and dermal unit exposures are acceptable grades. Hand = 31 replicates; and Dermal = 16 to 22 replicates. High confidence in dermal and hand data. Gloves were worn during the use of the engineering controls. No protection factor was needed to define the unit exposure value.
Loading Granular Formulations (2)	PHED V1.1	80 acres for tractor drawn spreaders for most crops; 40 acres for golf course turf	**Baseline:** Hand = all grades; dermal = acceptable grades; and inhalation = acceptable grades. Hands = 10 replicates; dermal = 29 to 36 replicates; and inhalation = 58 replicates. Low confidence in dermal/ hand data. High confidence in inhalation data. No protection factor was needed to define the unit exposure value. **PPE**: The available dermal data were coupled with a 50% protection factor to account for an additional layer of clothing. Hand = acceptable grades and dermal = ABC grades. Hands = 45 replicates; and dermal= 29 to 36 replicates. High confidence in dermal and hand data. **Engineering Controls:** Not required for assessment.
Applicator Descriptors			
Applying Sprays with a Groundboom Sprayer (3)	PHED V1.1	80 acres in agricultural settings and 40 acres on golf course turf	**Baseline:** Hand, dermal, and inhalation acceptable grades. Hands = 29 replicates, dermal = 32 to 42 replicates, and inhalation = 22 replicates. High confidence in hand, dermal, and inhalation data. No protection factor was required to define the unit exposure value. **PPE:** The same dermal data are used as for the baseline coupled with a 50% protection factor to account for an additional layer of clothing. Hand = ABC grades. Hands = 21 replicates. Medium confidence in dermal/ hand data. **Engineering Controls:** Hand and dermal = ABC grades. Hands= 16 replicates and dermal = 20 to 31 replicates. Medium confidence in hand and dermal data.

Table 10: Exposure Scenario Descriptions for the Use of Bensulide

Exposure Scenario (Number)	Data Source	Standard Assumptions[a] (8-hr work day)	Comments[b]
Applying Granulars with a Tractor Drawn Spreader (4)	PHED V1.1	40 acres for golf course turf	**Baseline:** Hands, dermal, and inhalation = acceptable grades. Hands = 5 replicates; dermal = 1 to 5 replicates; and inhalation = 5 replicates. Low confidence in hand, dermal, and inhalation data. No protection factor was required to define the unit exposure value. **PPE:** The same dermal and hand data are used as for the baseline coupled with a 50% protection factor to account for an additional layer of clothing and a 90% protection factor to account for the use of chemical resistant gloves. **Engineering Controls:** Hand and dermal = acceptable grades. Hands = 24 replicates and dermal = 2-30 replicates. Low confidence in hand/dermal data.
Mixer/Loader/Applicator Descriptors			
Mixing/Loading/Applying with a Low Pressure Handwand (5)	PHED V1.1	5 acres for occupational uses	**Baseline:** Hand and dermal = All grades and inhalation = All grades. Hand = 70 replicates, dermal = 25-96 replicates, and inhalation = 96 replicates. Low confidence in hand, dermal, and inhalation data. No protection factor was required to define the unit exposure value. **PPE:** The same dermal data are used as for the baseline coupled with a 50% protection factor to account for an additional layer of clothing . Hand data are acceptable grade. Hand = 15 replicates. Low confidence in dermal/hand data. **Engineering Controls:** Not feasible
Mixing/Loading/Applying with a High Pressure Handwand (6)	PHED V1.1	1,000 gallons	**Baseline:** Hand and dermal = ABC grades. Hands = 13 replicates; dermal = 7-13 replicates; and inhalation = 13 replicates. Low confidence in hand, dermal, and inhalation data. Baseline data includes chemical-resistant gloves. No protection factor was required to define the unit exposure value. **PPE:** The same dermal data are used as for the baseline coupled with a 50% protection factor to account for an additional layer of clothing . **Engineering Controls:** Not feasible

Table 10: Exposure Scenario Descriptions for the Use of Bensulide

Exposure Scenario (Number)	Data Source	Standard Assumptions[a] (8-hr work day)	Comments[b]
Mixing/Loading/Applying with a Backpack Sprayer (7)	PHED V1.1	5 acres for occupational uses	**Baseline:** Hands and dermal = ABC grades; and inhalation = acceptable grades. Hands = 11 replicates; dermal = 9-11 replicates; and inhalation = 11 replicates. Low confidence in hand, dermal, and inhalation data. Baseline data includes chemical-resistant gloves. No protection factor was required to define the unit exposure value. **PPE:** The same dermal and hand data are used as for the baseline coupled with a 50% protection factor to account for an additional layer of clothing. **Engineering Controls:** Not feasible
Mixing/Loading/Applying with a Handgun (turf grass application) (8)	PHED V1.1	5 acres for occupational uses.	Data for open mixing of liquids and handgun turfgrass application were combined to generate mixer/loader/applicator value as this is the most likely exposure scenario. **Baseline for mixer/loader:** see PHED data for open mixing/loading liquids (Exposure Scenario 1) **Baseline for application:** Hand and dermal = all grades; and inhalation = acceptable grades. Hand = 14 replicates; dermal = 0-14 replicates; and inhalation = 14 replicates. Low confidence in hand and dermal data. Inhalation data are low to medium confidence. Baseline dataset was based on the use of chemical-resistant gloves. Therefore, a reverse 90% PF was used on the gloved hand data to assess baseline exposure for individuals wearing no gloves. **PPE for mixer/loader:** see PHED data for open mixing/loading liquids (Exposure Scenario 1). A 50% protection factor used to account for a single layer of clothing was required to define the unit exposure value. **PPE for applicator:** The same dermal and hand data are used as for the baseline coupled with a 50% protection factor to account for an additional layer of clothing. **Engineering Controls:** Not feasible.

Table 10: Exposure Scenario Descriptions for the Use of Bensulide

Exposure Scenario (Number)	Data Source	Standard Assumptions[a] (8-hr work day)	Comments[b]
Mixing/Loading/Applying with a Push-Type Granular Spreader (9)	PHED V1.1	0.5 acre for homeowners 5 acres for occupational uses.	**Baseline:** Hand and dermal =A,B,C grades; and inhalation = acceptable grades. Hand = 15 replicates; dermal = 0 to 15 replicates; and inhalation = 15 replicates. Low to medium confidence in the dermal and hand data. High confidence in the inhalation data. No protection factor was required to define the unit exposure scenario. **PPE:** The same dermal and hand data are used as for the baseline coupled with a 50% protection factor to account for an additional layer of clothing and a 90% protection factor to account for the use of chemical resistant clothing. **Engineering Controls:** Not feasible.
Mixing/Loading/Applying with a Bellygrinder (10)	PHED V1.1	0.5 acre for homeowners 5 acres for occupational uses.	**Baseline:** Hand and dermal = A, B, C grades; and inhalation = acceptable grades. Hand = 23 replicates; dermal = 29-45 replicates; and inhalation = 40 replicates. Medium confidence in hand and dermal data. High confidence in inhalation data. No protection factor was required to define the unit exposure. **PPE:** The same dermal data are used as for the baseline coupled with a 50% protection factor to account for an additional layer of clothing. Hand = A, B, C grades. Hands = 15 replicates. Medium confidence in the hand data. **Engineering Controls:** Not feasible.

[a] All *Standard Assumptions* are based on an 8-hour work day as estimated by HED. BEAD data were not available.

[b] All handler exposure assessments in this document are based on the "Best Available" data as defined by the PHED SOP for meeting Subdivision U Guidelines (i.e., completing exposure assessments). Best available grades are assigned to data as follows: matrices with A and B grade data (i.e., Acceptable Grade Data) and a minimum of 15 replicates; if not available, then grades A, B and C data and a minimum of 15 replicates; if not available, then all data regardless of the quality (i.e., All Grade Data) and number of replicates. High quality data with a protection factor take precedence over low quality data with no protection factor. Generic data confidence categories are assigned as follows:

High = grades A and B and 15 or more replicates per body part
Medium = grades A, B, and C and 15 or more replicates per body part
Low = grades A, B, C, D and E or any combination of grades with less than 15 replicates.

iv. Post-Application Exposure Scenarios and Assumptions

HED evaluated bensulide use patterns in the agricultural marketplace and determined that the potential for post-application agricultural worker exposure is low due to the timing of applications and given the mode of action as a herbicide (i.e., watered in and sometimes soil incorporated). In agricultural settings, bensulide is applied as a pre-plant or pre-emergent herbicide. "The herbicidal activity of bensulide is highly dependent on watering the material into the soil soon after application, so it is used almost entirely on irrigated crops and on turf into which it can be watered." Additionally, when applied pre-plant in agricultural settings, bensulide is soil incorporated. This is generally well before the plants are mature which minimizes the potential for post-application exposure due to contact from treated foliage. Likewise, high exposure activities associated with the use of bensulide are not anticipated because the activities related to the cultivation of the target agricultural crops, early in the season when bensulide is typically applied, are limited and typically do not require intense contact with treated areas. However, to ensure that this assessment is adequate, further information pertaining to the use of bensulide and any cultural practices associated with the crops in question should be provided in order for HED to assess any scenarios where there is exposure potential (e.g., hand transplanting where extensive contact with treated soil may be required). Additionally, there are no apparent sod farm uses so this occupational exposure scenario was not considered in this assessment.

HED evaluated bensulide use patterns in the ornamental and residential marketplaces and determined that there are likely post-application exposures because bensulide is routinely applied to established lawns and to areas such as golf courses. HED believes that post-application exposures due to inhalation will be minimal. As a result, only dermal exposures were evaluated for this assessment. In addition, non-dietary ingestion (as a result of toddler or golfer hand-to-mouth contact) was not considered. Based on the anticipated bensulide use patterns and current labelling, four major post-application exposure scenarios for bensulide were modelled using a surrogate approach. Two of these scenarios are assessments of exposure to adults while the remaining two scenarios were assessments of exposures to toddlers. These assessments were based on the guidance provided in the *Draft: Series 875-Occupational and Residential Exposure Test Guidelines, Group B-Postapplication Exposure Monitoring Test Guidelines (7/24/97 Version)* and the *Draft: Standard Operating Procedures (SOPs) for Residential Exposure Assessment (12/11/97 Version)*. The four scenarios that were assessed include the following:

(1) adults involved in a low exposure activity at the lowest prescribed application rate for turf ;

(2) adults involved in a high exposure activity at the highest application rate for turf;

(3) toddlers involved in a high exposure activity at the lowest prescribed application rate for turf; and

(4) toddlers involved in a high exposure activity at the highest prescribed application rate for turf.

The dose levels calculated for adults were used for establishing restricted entry intervals for adults engaged in activities related to occupational turf management. The adult dose levels calculated for these scenarios also served as the basis for the residential aggregate risk assessment. Toddler levels were calculated solely for the residential exposure assessment for the purpose of aggregation.

The following specific assumptions and factors were used in order to complete this exposure assessment:

- MOEs for adults in the occupational scenarios (e.g., turf management) were calculated using the intermediate-term endpoint, since the intermediate exposure scenario is likely based on the environmental fate characteristics of bensulide. The EFED *One-Liner Database* was checked and the $t_{½}$ is 220 days (solar days) based on soil photolysis; 200 days for aqueous photolysis; and 220 to 230 days for hydrolysis.

- Due to a lack of chemical-specific transferable residue data (TR), a surrogate approach has been used to predict transferable residue levels over time as specified in the residential SOPs. Available residues on application day are assumed to be 20 percent of the application rate and the residues are assumed to decline at a rate of 10 percent per day. [Note: This is not a conservative approach based on the available data presented above that describes the environmental fate characteristics of bensulide.]

- The average body weight for adults used in all assessments is 70 kg based on current HED policy. This body weight is used in the intermediate-term assessment, since the endpoint of concern is not sex-specific. The average body weight for toddlers used in all assessments is 15 kg based on the residential SOPs.

- A typical occupational work day interval is generally considered 8 hours. However, since the primary concern for post-application bensulide exposure is non-agricultural occupational, and non-occupational exposure to treated turf (e.g., golf courses and residential), the daily exposure interval for the assessment is assumed to be 4 hours/day for adults and 2 hours/day for toddlers (the toddler value is presented in the residential SOPs). These values are believed to be reasonable high end estimates for time spent engaged in specific activities.

- Calculations are completed at the minimum and maximum application rates recommended by the available bensulide labels to bracket risk levels associated with the various use patterns and activity scenarios. No use data were provided by the registrant concerning actual application rates. The minimum application rate is based on Reg. No.10163-204-33955 while maximum application rate is based on Reg. No. 10163-198-2217 (as well as several others).

- Due to a lack of scenario-specific exposure data, HED has calculated unit exposure values for adults using surrogate dermal transfer coefficients that represent reasonable low (1,000

cm^2/hour) and high exposure activities (10,000 cm^2/hour) such as mowing, golfing, and yardwork. [Note: The transfer coefficient prescribed in the residential SOPs for this scenario for adults is 43,000 cm^2/hour. Lower transfer coefficient values were selected for this assessment (i.e., 1,000 and 10,000 cm^2/hour) so that the dose levels could also be used by HED for the occupational assessment and because the calculated risk levels were unacceptable even at these relatively modest transfer coefficient values. Based on the residential SOPs, a transfer coefficient of 8,700 cm^2/hour was used to calculate dermal exposures for toddlers. [Note: The transfer coefficient for toddler exposures is likely to be conservative. However, the calculated exposures do not include Incidental Nondietary Ingestion levels as prescribed in the residential SOPs.]

v. Post Application Exposure Assessment

The calculations presented in this section serve as the basis for both the short-term and intermediate-term post-application risk assessments. No chemical-specific post-application human reentry or transferable residue data have been submitted to date in support of the reregistration of bensulide. Therefore, a surrogate post application exposure assessment was conducted to determine potential risks for four representative scenarios, and the data are presented in Tables 12 and 13. The oxygen analogue of bensulide was not considered in these assessments. Table 11 contains adult dose and MOE values for occupational scenarios. As noted above, these dose levels were also used for calculation of aggregate risks. This assessment was completed using a restricted entry interval approach in which MOE values were calculated for each day after application until an acceptable level of risk was obtained (i.e., an MOE > 100). It should be noted that the adult exposure scenarios (i.e., scenarios 1 and 2) are presented in this manner to illustrate risk concerns over bensulide use on turf for those occupationally exposed.

Doses attributable to various exposure routes and pathways must be aggregated according to the *Food Quality Protection Act* for calculating risks in the residential environment. The exposure scenarios for toddlers described above (i.e., scenarios 3 and 4) served as the basis for modeling normalized dose levels over a 30 day period after bensulide applications at the lowest and highest rates to turf. Dose levels were then calculated as described in the residential SOPs. Both the calculation of surrogate transferable residue levels and the corresponding dose levels are presented in Table 12. [Note: This approach is likely to be conservative. However, it should also be noted that incidental ingestion and inhalation exposures are not included in the calculation.] The next step in the process was to evaluate the calculated dose levels and determine the appropriate value for use in the aggregation process. For short-term exposures, post-application day 0 dose levels were used. On the other hand, it was decided that, for intermediate-term exposure, an average dose level calculated by using all values over the 30 day period after a single application will be used because bensulide appears to be quite persistent and it is likely to be used only once per season on turf because of its herbicidal activity (i.e., additivity over several months of applications was not considered).

The surrogate assessment for adults in which margins of exposure and restricted entry intervals were calculated is based on the assumptions described above, the toxicological endpoint

appropriate for intermediate-term exposure [NOEL of 0.50 mg/kg/day, based on inhibition of plasma (males and females) and brain (males) cholinesterase activities at 4.0 mg/kg/day in a chronic toxicity study in dogs in which inhibition of plasma cholinesterase activities were observed at the earliest time point of measurement, 13 weeks], and a 20 percent dermal absorption value (DA). Additionally, the following equations served as the basis for all aspects of the surrogate post-application assessment:

- Application day transferable residue levels (TR) were calculated as follows:

  $TR_{APP.\ DAY}$ ($\mu g/cm^2$) =

  (AR (lb ai/acre)*TR (%/100)*4.54E8 (μg/lb))/(43560 (ft^2/acre)*929 (cm^2/ft^2)

  Where:
  AR =Application Rate; and
  $TR_{APP.\ DAY}$=Transferable Residue on application day.

- Transferable residue levels (TR) on each day subsequent to application were calculated as follows:

  $TR_{(t)}$ ($\mu g/cm^2$) = $TR_{APP.\ DAY}$ ($\mu g/cm^2$) * $(1\text{-}D)^t$

  Where:
  $TR_{APP.\ DAY}$= Transferable Residue on application day;
  $TR_{(t)}$ = Transferable Residue at time (t);
  D = fraction of residue that dissipates daily (%/100); and
  t = post application day on which exposure is being assessed (day).

- Dermal Dose values on each post-application exposure day were calculated using the following:

  Dermal $Dose_{(t)}$ (mg/kg/day) =

  ($TR_{(t)}$ ($\mu g/cm^2$) x TC (cm^2/hr)x DA (%/100) x Hr/Day)/(BW (kg) x 1000 (μg/mg))

  Where:
  TR = Transferable Residue,
  TC = Transfer Coefficient,
  DA = Dermal Absorption,
  Hr = Hours, and
  BW = Body Weight.

- MOEs on each post-application exposure day were calculated using the following:

$MOE_{(t)}$ = NOEL (mg/kg/day)/Dermal $Dose_{(t)}$ (mg/kg/day)

Table 11. Occupational Dose and Restricted Entry Intervals

DAYS AFTER TREATMENT	TRANSFERABLE (ug/cm2)		ADULT DOSE (mg/kg/day)		ADULT MOE	
	MIN. ORN RATE	MAX. ORN RATE	LOW TC	HIGH TC	LOW TC	HIGH TC
			MIN. ORN	MAX ORN	MIN. ORN	MAX ORN
0	16.828	28.047	0.192	3.205	3	<1
1	15.146	25.243	0.173	2.885	3	<1
2	13.631	22.718	0.156	2.596	3	<1
3	12.268	20.447	0.140	2.337	4	<1
4	11.041	18.402	0.126	2.103	4	<1
5	9.937	16.562	0.114	1.893	4	<1
6	8.943	14.906	0.102	1.703	5	<1
7	8.049	13.415	0.092	1.533	5	<1
8	7.244	12.073	0.083	1.380	6	<1
9	6.520	10.866	0.075	1.242	7	<1
10	5.868	9.780	0.067	1.118	7	<1
11	5.281	8.802	0.060	1.006	8	<1
12	4.753	7.921	0.054	0.905	9	<1
13	4.278	7.129	0.049	0.815	10	<1
14	3.850	6.416	0.044	0.733	11	<1
15	3.465	5.775	0.040	0.660	13	<1
16	3.118	5.197	0.036	0.594	14	<1
17	2.807	4.678	0.032	0.535	16	<1
18	2.526	4.210	0.029	0.481	17	1
19	2.273	3.789	0.026	0.433	19	1
20	2.046	3.410	0.023	0.390	21	1
21	1.841	3.069	0.021	0.351	24	1
22	1.657	2.762	0.019	0.316	26	2
23	1.491	2.486	0.017	0.284	29	2
24	1.342	2.237	0.015	0.256	33	2
25	1.208	2.014	0.014	0.230	36	2
26	1.087	1.812	0.012	0.207	40	2
27	0.979	1.631	0.011	0.186	45	3
28	0.881	1.468	0.010	0.168	50	3
29	0.793	1.321	0.009	0.151	55	3
30	0.713	1.189	0.008	0.136	61	4
DAYS AFTER TREATMENT	TRANSFERABLE (ug/cm2)		ADULT DOSE (mg/kg/day)		ADULT MOE	
	MIN. ORN RATE	MAX. ORN RATE	LOW TC	HIGH TC	LOW TC	High TC
			MIN. ORN	MAX. ORN	MIN. ORN	MAX. ORN
31	0.642	1.070	0.007	0.122	68	4
32	0.578	0.963	0.007	0.110	76	5
33	0.520	0.867	0.006	0.099	84	5
34	0.468	0.780	0.005	0.089	93	6
35	0.421	0.702	0.005	0.080	104	6
36	N/A	0.632	N/A	0.072	N/A	7
37	N/A	0.569	N/A	0.065	N/A	8

Table 11 (Continued)

38	N/A	0.512	N/A	0.058	N/A	9
39	N/A	0.461	N/A	0.053	N/A	9
40	N/A	0.415	N/A	0.047	N/A	11
41	N/A	0.373	N/A	0.043	N/A	12
42	N/A	0.336	N/A	0.038	N/A	13
43	N/A	0.302	N/A	0.035	N/A	14
44	N/A	0.272	N/A	0.031	N/A	16
45	N/A	0.245	N/A	0.028	N/A	18
46	N/A	0.220	N/A	0.025	N/A	20
47	N/A	0.198	N/A	0.023	N/A	22
48	N/A	0.178	N/A	0.020	N/A	25
49	N/A	0.161	N/A	0.018	N/A	27
50	N/A	0.145	N/A	0.017	N/A	30
51	N/A	0.130	N/A	0.015	N/A	34
52	N/A	0.117	N/A	0.013	N/A	37
53	N/A	0.105	N/A	0.012	N/A	42
54	N/A	0.095	N/A	0.011	N/A	46
55	N/A	0.085	N/A	0.010	N/A	51
56	N/A	0.077	N/A	0.009	N/A	57
57	N/A	0.069	N/A	0.008	N/A	63
58	N/A	0.062	N/A	0.007	N/A	70
59	N/A	0.056	N/A	0.006	N/A	78
60	N/A	0.050	N/A	0.006	N/A	87
61	N/A	0.045	N/A	0.005	N/A	96
62	N/A	0.041	N/A	0.005	N/A	107

INPUT PARAMETERS			APPL. RATE (lb ai/A)	
TRANSFERABLE (%):	20		MIN. ORN	MAX ORN
DAILY DISSIPATION (%):	10		7.5	12.5
LOW ADULT TC (cm2/hr):	1000			
HIGH ADULT TC (cm2/hr):	10000		DAY 0 TO 30 MEANS	
DERMAL ABSORPTION (%):	20		(mg/kg/day)	
ADULT BODY WEIGHT (kg):	70		LOW TC	0.06
TOX. ENDPOINT (mg/kg/day):	0.5		HIGH TC	0.995
ADULT HR/DAY:	4			

Table 12. Post-Application Dose Levels for Toddlers

DAYS AFTER TREATMENT	DFR (ug/cm2)		TODDLER DOSE (mg/kg/day)	
	MIN. ORN	MAX. ORN	SOP TC MIN. ORN	SOP TC MAX. ORN
0	16.83	28.05	3.90	6.51
1	15.15	25.24	3.51	5.86
2	13.63	22.72	3.16	5.27
3	12.27	20.45	2.85	4.74
4	11.04	18.40	2.56	4.27
5	9.94	16.56	2.31	3.84
6	8.94	14.91	2.07	3.46
7	8.05	13.42	1.87	3.11
8	7.24	12.07	1.68	2.80
9	6.52	10.87	1.51	2.52
10	5.87	9.78	1.36	2.27
11	5.28	8.80	1.23	2.04
12	4.75	7.92	1.10	1.84
13	4.28	7.13	0.99	1.65
14	3.85	6.42	0.89	1.49
15	3.46	5.77	0.80	1.34
16	3.12	5.20	0.72	1.21
17	2.81	4.68	0.65	1.09
18	2.53	4.21	0.59	0.98
19	2.27	3.79	0.53	0.88
20	2.05	3.41	0.47	0.79
21	1.84	3.07	0.43	0.71
22	1.66	2.76	0.38	0.64
23	1.49	2.49	0.35	0.58
24	1.34	2.24	0.31	0.52
25	1.21	2.01	0.28	0.47
26	1.09	1.81	0.25	0.42
27	0.98	1.63	0.23	0.38
28	0.88	1.47	0.20	0.34
29	0.79	1.32	0.18	0.31
30	0.71	1.19	0.17	0.28
MEANS	N/A	N/A	1.21	2.02

DFR = DISLODGEABLE FOLIAR RESIDUE

SOP TC = DERMAL TC FROM RESIDENTIAL SOPS

MIN. OR MAX. ORN = RANGE OF ORNAMENTAL APP. RATES

INPUT PARAMETERS	
TRANSFERABLE (%):	20
DAILY DISSIPATION (%):	10
CHILD SOP TC (cm2/hr):	8700
DERMAL ABSORPTION (%):	20

CHILD BODY WEIGHT (kg):	15
CHILD HR/DAY:	2
MAX. APPL. RATE (lb ai/A):	12.5
MIN. APPL. RATE (lb ai/A):	7.5

4.b. Occupational and Residential Risk Assessment/Characterization

i. Methods For Calculating Risks from Occupational Dermal and Inhalation Exposures

The daily dermal dose has been calculated using a 60 kg body weight for short-term exposures and a 70 kg body weight for intermediate-term exposures for handlers. All toxicological endpoints used to assess risks from dermal exposure are based on oral administration of bensulide. No chemical-specific dermal absorption data are available. Therefore, a dermal absorption value of 20 percent that has been estimated based on the ratio of the acute dermal and acute oral endpoints is used in all calculations. Daily dermal dose was calculated using the following formula:

$$Daily\ Dermal\ Dose\left(\frac{mg\ ai}{kg/day}\right) = Daily\ Dermal\ Exposure\left(\frac{mg\ ai}{day}\right) x \left(\frac{DermalAbsorptionFactor(\%/100)}{Body\ Weight\ (kg)}\right)$$

The calculations of daily dermal dose received by handlers are used to assess the dermal risk to handlers (see Section 4.a. for explanation of the calculation of Daily Dermal Exposure). The short-term dermal MOEs were calculated using a NOEL of 5.5 mg/kg/day, and the intermediate-term dermal MOEs were calculated using a NOEL of 0.5 mg/kg/day. The short-term and intermediate-term dermal MOEs were calculated using the following formula:

$$MOE = \frac{NOEL\left(\frac{mg}{kg/day}\right)}{Daily\ Dermal\ Dose\left(\frac{mg}{kg/day}\right)}$$

The calculations used to estimate *Daily Dermal Dose* and *MOE* for the dermal post-application scenarios are similar. The only significant difference is the manner in which the *Daily Dermal Exposure* is calculated using a transfer coefficient, transferable residue levels, and accounting for the dissipation of bensulide over time [see Section **4. a. iv. (Post Application Exposure Assessment)** for further details]. For occupational scenarios, *Daily Dermal Dose* and *MOE* values were calculated for each post application day until a reentry interval was achieved based on the MOE value (i.e., REIs are based on MOE values $\geq$ 100). For aggregation purposes, Daily Dermal Dose Values for up to 30 days were used in this assessment.

The calculations of airborne bensulide concentrations are used to assess the inhalation risks to handlers. Daily inhalation exposure levels were calculated for inclusion into the PHED surrogate exposure tables and presented as (μg/lb ai) based on a human inhalation rate of 29 L/minute and an 8 hour working day. However, the risk calculations presented in this document are based on a

direct comparison of the concentration-based inhalation endpoint and a time-weighted average (TWA) inhalation air concentration associated with a particular exposure scenario (mg/L). To reiterate, the TWA concentration values were calculated as follows:

Inhalation Air Concentration (mg/L) =

$$\frac{\text{Unit exposure (µg ai/lb ai) x Use Rate (lb ai/A) x Daily Acres Treated (A/day)}}{13.92\ m^3/day \times 1000 µg/mg \times 1000\ L/m^3}$$

[Note: The daily inhalation rate of 13.92 m^3/day is based on the following calculation. (29 L/min x 60 min/hr x 8 hr/day)/(1 m^3/ 1000 L).]

After calculation of the TWA inhalation air concentration, the handler inhalation MOEs for bensulide are calculated using an inhalation concentration of 1.75 mg/L and the following:

$$MOE = \frac{Inhalation\ Concentration\left(\frac{mg}{L}\right)}{Inhalation\ Air\ Conc.\left(\frac{mg}{L}\right)}$$

ii. General Risk Characterization Considerations

Several issues must be considered when interpreting the occupational and residential exposure (ORE) and risk assessment. These include:

- No chemical-specific exposure or transferable residue data were submitted. As a result, all analyses were completed using surrogate data from sources such as PHED and assumptions related to the behavior of the chemical in the environment (e.g., dissipation of transferable residues on turf).

- Several handler assessments were completed using "low quality" PHED data due to the lack of a more appropriate dataset.

- Several generic protection factors were used to calculate handler exposures. These protection factors have not been completely evaluated and accepted by HED.

- Factors used to calculate daily exposures to handlers and for the post-application scenarios (e.g., hours per day for post-application exposure or acres treated per day for each application method) are based on the best professional judgement due to a lack of pertinent data.

- The transfer coefficients used to calculate post-application dermal exposures are generic in nature due to a lack of time-based activity pattern data pertinent to the residential

environment and the applicable transfer coefficients. The two transfer coefficients are believed to represent typical low and high exposure activities for the exposed populations.

- A value of 20 percent was estimated by HED based on the ratio of the acute dermal and oral endpoints. Since the dermal LD_{50} was greater than 2000 mf/kg body weight/day, this estimate may exceed the actual dermal absorption of bensulide.

Refinement of the ORE exposure and risk assessment calculations presented in this chapter is possible if the issues presented above are addressed by the registrant or if more refined approaches or data become available to HED.

iii. Dermal Risk from Handler Exposures

Dermal risks for handlers were assessed using the short-term and intermediate-term toxicological endpoints. Results from each assessment are presented below (i.e., Short-term assessment followed by Intermediate-Term assessment). A chronic risk assessment was not completed as the HED believes that bensulide use patterns do not lend themselves to chronic exposure scenarios. All risk characterizations presented below are **occupational** in nature unless noted.

Short-Term Dermal Handler Risks

The calculations of short-term dermal risk indicate that the MOEs are more than 100 at **baseline** for the following scenarios:

- (2) loading granulars for tractor-drawn spreader application on turf and ornamentals at all application rates up to and including the maximum 12.5 pound ai per acre rate (based on low confidence data and no protection factors);

- (3) applying sprays with an opencab groundboom sprayer on agricultural crops at all application rates up to and including the maximum 6.0 pound ai per acre rate and on turf and ornamentals at all application rates up to and including the maximum 12.5 pound ai per acre rate (based on high confidence data and no protection factors);

- (4) applying granulars with an opencab tractor drawn spreader to turf and ornamentals at all application rates up to and including the maximum 12.5 pound ai per acre rate (based on low confidence data and no protection factors); and

- (9) homeowner loading and applying granulars with a push-type granular spreader to turf and ornamentals at the lowest application rate of 7.5 pound ai per acre rate (based on low to medium confidence data and no protection factors).

The calculations of short-term dermal risk indicate that the MOEs are more than 100 with **additional PPE** for the following scenarios:

- (1b) mixing/loading liquids for groundboom application on agricultural crops at all application rates up to and including the maximum 6.0 pound ai per acre rate and on turf and ornamentals at all application rates up to and including the maximum 12.5 pound ai per acre rate (based on high confidence data and no protection factors);

- (1c) mixing/loading liquids for professional application to turf and ornamentals using a low pressure/high volume handgun at all application rates up to and including the maximum 12.5 pound ai per acre rate (based on high confidence data and no protection factors); and

- (8) mixing/loading and applying liquids with a low pressure/high volume handgun at all application rates up to and including the maximum 12.5 pound ai per acre rate (based on low confidence data and the use of protection factors).

The calculations of short-term dermal risk indicate that the MOEs are more than 100 with **engineering controls** for the following scenarios:

- (1a) mixing/loading liquids for chemigation application on agricultural crops at all application rates up to and including the maximum 6.0 pound ai per acre rate (based on high confidence data and no protection factors).

The calculations of short-term dermal risk indicate that the MOEs are not more than 100 despite the maximum mitigation measures for the remainder of the scenarios.

Intermediate-Term Dermal Handler Risk

The calculations of intermediate-term dermal risk indicate that the MOEs are more than 100 at **baseline** for the following scenarios:

- none

The calculations of intermediate-term dermal risk indicate that the MOEs are more than 100 with **additional PPE** for the following scenarios:

- (2) loading granulars for tractor-drawn spreader application on turf and ornamentals at all application rates up to and including the maximum 12.5 pound ai per acre rate (based on medium confidence data and the use of protection factors); and

- (4) applying granulars with an opencab tractor drawn spreader to turf and ornamentals at the minimum application rate of 7.5 pound ai per acre rate (based on low confidence data and the use of protection factors).

The calculations of intermediate-term dermal risk indicate that the MOEs are more than 100 with **engineering controls** for the following scenarios:

- (3) applying sprays with an closed cab groundboom sprayer on agricultural crops at the minimum application rate of 3.0 pound ai per acre rate (based on medium confidence data and no protection factors); and

- (4) applying granulars with an closed cab tractor-drawn spreader to turf and ornamentals at the maximum application rate of 12.5 pound ai per acre rate (based on low confidence data and no protection factors).

The calculations of intermediate-term dermal risk indicate that the MOEs are not more than 100 despite the maximum mitigation measures for the remainder of the scenarios.

iv. Inhalation Risk from Handler Exposures

Inhalation risks for handlers were assessed using a single toxicological endpoint based on the LC_{50} value obtained in an acute inhalation study in rats. A chronic risk assessment was not completed as the HED believes that bensulide use patterns do not lend themselves to chronic exposure scenarios. The calculations of inhalation risk indicate that the MOEs are more than 100 at **baseline** for all exposure scenarios and all application rates.

v. Intermediate-Term Dermal Occupational Risk From Post-Application Exposures

Given the current state of knowledge, HED does not consider post application exposure in agricultural settings problematic due to the cultivation practices that are anticipated with the pre-plant/pre-emergent use of bensulide on the labelled agricultural crops (i.e., the WPS prescribed reentry interval is adequate). This evaluation is based on an assessment of bensulide labelling and available use information. However, HED requests that additional information be submitted pertaining to cultural practices of the labelled crops in order to refine this assessment.

Short-term dermal occupational risks (in non-agricultural scenarios, such as turf management) from post application exposure were not calculated because no chemical-specific data were available to quanitify transferable residues and the exposure scenario more likely is an intermdiate-term pattern. The EFED database supports this possibility in that it indicates half-lives of approximately 200 days (soil and hydrolysis) for bensulide. Inhalation exposures were also not included because such exposures are considered to be minimal by HED.

The occupational restricted entry intervals on turf were calculated using various assumptions as indicated above based on the lack of chemical-specific data and the most sensitive dermal toxicological endpoint. This surrogate postapplication exposure assessment indicates that:

- On turf in occupational settings, at an application rate of 7.5 pounds active ingredient per acre, MOEs equal or exceed 100 for activities on turf with potentially **low** dermal transfer 35 days following a single application (based on assumptions by HED concerning chemical dissipation and transfer coefficient, no chemical-specific data were available); and

- On turf in occupational settings, at an application rate of 12.5 pounds active ingredient per acre, MOEs did not equal or exceed 100 for activities on turf with potentially **high** dermal transfer 62 days following a single application (based on surrogate data, no chemical-specific data were available).

vi. Intermediate-Term Non-Occupational Dermal Risks from Post-Application Exposures

The NOEL used for intermediate-term exposures to bensulide is 0.50 mg/kg/day, based on inhibition of plasma (males and females) and brain cholinesterase (males) activities at 4.0 mg/kg/day in a chronic toxicity study in dogs in which effects on plasma cholinesterase activities were observed as early as 13 weeks. For this calculation, the average dose level over a 30-day period was used for both toddlers and adults, since bensulide residues are likely to be persistent. As shown for adults in Table 11, for low exposure (LE) activities on turf treated with the lowest prescribed application rate (LA) of bensulide, or for high exposure (HE) activities on turf treated with the highest prescribed application rate (HA), the MOEs for 30-day post-application average intermediate-term dermal non-occupational exposures are:

Adult: MOE = $\frac{0.50 \text{ mg/kg/day (NOEL)}}{0.060 \text{ mg/kg/day}} = 8$
(LE; LA)

Adult: MOE = $\frac{0.50 \text{ mg/kg/day (NOEL)}}{0.995 \text{ mg/kg/day}} < 1$
(HE; HA)

Based on Table 12, for high exposure (HE) activities on turf treated with bensulide at the lowest (LA) or highest (HA) prescribed application rates, the MOEs for the 30-day average intermediate-term dermal non-occupational risks for toddlers are:

Children: MOE = $\frac{0.50 \text{ mg/kg/day (NOEL)}}{1.211 \text{ mg/kg/day}} < 1$
(HE; LA)

Children: MOE = $\frac{0.50 \text{ mg/kg/day (NOEL)}}{2.019 \text{ mg/kg/day}} < 1$
(HE; HA)

All of these MOEs are unacceptable, since they are far less than the value of 100, which is

generally regarded as acceptable by the Agency.

vii. Short-Term Non-Occupational Dermal Risks from Post-Application Exposures

For short-term risks to adults , the exposure levels shown in Table 11 for Day 0 were used and the MOEs were calculated using the NOEL (5.5 mg/kg/day) for inhibition of maternal plasma cholinesterase activity observed in developmental toxicity study in rats. Surrogate exposures for Day 0 have been used because there are no actual data on post-application concentrations of bensulide as a function of time for bensulide-treated lawns and expected bensulide concentrations on treated turf over the short term (1-7 days) would be maximal at this time period.

For both high exposure (HE) activities on turf treated with the highest prescribed application rate (HA) for bensulide for turf, and for low exposure (LE) activities on turf treated with the lowest prescribed application rate (LA) of bensulide, the following MOEs may be calculated for adults:

Adults: MOE = 5.5 mg/kg/day (NOEL) = 2
(HE; HA) 3.205 mg/kg/day

Adults: MOE = 5.5 mg/kg/day (NOEL) = 29
(LE; LA) 0.192 mg/kg/day

For short-term risks to toddlers, the dose levels shown in Table 12 for Day 0 were used and the MOEs were calculated for both the lowest (LA) and highest (HA) prescribed application rates for bensulide treatment of turf. For toddlers, a single high exposure rate (HE; TC from Residential SOPs) was used. The following MOEs were calculated for toddlers:

Children: MOE = 5.5 mg/kg/day (NOEL) < 1
(HE; HA) 6.51 mg/kg/day

Children: MOE = 5.5 mg/kg/day (NOEL) = 1
(HE; LA) 3.90 mg/kg/day

All of these MOEs are unacceptable, since they are far less than the value of 100, which is generally regarded as acceptable by the Agency.

vii. Incident Reports

EPA obtained incident information concerning bensulide from three sources: the Office of Pesticide Programs (OPP) Incident Data System (IDS), the California Department of Food and Agriculture (CFDA; replaced by the Department of Pesticide Regulation in 1991), and the National Pesticide Telecommunications Network (NPTN; a toll-free information service

supported by OPP). The IDS contains reports of incidents from various sources, including registrants, other federal and state health and environmental agencies, and individual consumers, submitted to OPP since 1992. The CFDA data consists of uniform reports, required by statute since 1982, from physicians on suspected pesticide poisonings and all illnesses suspected of being related to exposure to pesticides. The NPTN data consists of a tabulation of the top 200 active ingredients for which telephone calls were received during calendar years 1984-1991 into categories of human incidents, animals incidents, calls for information, and others. Bensulide was not included in the Data-Call-Ins issued by OPP in 1993 for 28 organophosphate and carbamate chemicals; therefore, no data were obtained from the Poison Control Centers on this chemical.

IDS Data

Two cases reported to the IDS involved individuals who were both exposed to bensulide in 1994 and experienced ocular irritation and pain. No further information on the dispositions of either of these two cases was reported.

CFDA Data

During the period from 1982 to 1995, 8 cases involving bensulide (6 of these involving exposure to bensulide alone) were reported. Two of these cases involved skin effects only, one dealt with eye effects only, and three were reported as systemic (not including skin or eye effects). Of the 6 persons exposed to bensulide alone, one person was reported as disabled (defined as taking time off from work) for more than 10 days, one person was disabled for an undefined period, and one person was hospitalized for 6-10 days. One of the 6 cases involved bensulide drift from non-target areas and one resulted from coincidental exposure. The remaining four cases were work-related and involved one mixloader and three applicators. The majority of these exposures were related to ground application of bensulide. Reported illnesses included symptoms of headaches, nausea, malaise, and nasal stuffiness. One of these six cases may have been changed from being regarded as pesticide-related to flu-related, but this could not be confirmed. Bensulide was ranked as 126th among pesticides as a cause of systemic poisoning in California.

NPTN Data

On the list of the top 200 chemicals for which NPTN received calls from 1984-1991 inclusive, bensulide was ranked 145th, with 19 incidents in humans reported and 3 in animals (mostly pets).

CONCLUSIONS

Very few illness cases have been reported due to bensulide, and none have been well confirmed.

5. AGGREGATE EXPOSURE AND RISK ASSESSMENT/ CHARACTERIZATION

In examining aggregate exposure, FQPA directs the Agency to consider the available, reliable information concerning exposures from pesticide residues in food, in drinking water whether from surface water or ground water, from residential uses in and around the home, and any other areas such as schools or recreational areas where the pesticide may be used. Due to a lack of pertinent monitoring data, exposures to bensulide due to ingestion of drinking water will be addressed by the Agency at a later date.

5.a. Acute Aggregate Exposure and Risk (Food Source)

The total acute dietary risk due to ingestion of bensulide-treated food has been estimated previously (Section III.B.3.c.iii.), and the subpopulations having the lowest MOEs for acute dietary risk from food sources are infants (<1 year) and children (1 to 6 years). The MOEs for both of these subpopulations are 1500 for exposures due to food ingestion. The acute dietary risk from food sources for the general population has a MOE of 3751. Therefore, the acute risks posed by bensulide to all population subgroups from food ingestion are all below the Agency's level of concern.

5.b. Short-term Aggregate Exposure and Risk

Short-term (1-7 days) aggregate exposures and risks from bensulide result from additional short-term exposures, such as those resulting from exposure to bensulide-treated residential lawns or golf courses, added to the chronic exposures due to dietary routes (food). Thus, for non-workers, short-term aggregate exposure and risk would represent the sum of exposures and risks due to chronic dietary (food) and short-term residential non-dietary oral, dermal and inhalation residential exposures to bensulide. However, as previously discussed, HED considers inhalation exposures to bensulide in non-occupational settings to be minimal. Non-dietary ingestion exposures due to hand-to-mouth activity were not considered in this assessment, given the overwhelming dermal exposures calculated for this scenario. Therefore, short-term aggregate exposure and risk for non-workers consist of the sum of chronic dietary exposure (via food ingestion) and additional short-term dermal residential exposures. Post-application exposures to bensulide for non-workers are expected following use on residential turf or ornamentals or on golf course turf. Small children playing on lawns treated with bensulide would be of special concern.

For adults or children pursuing high exposure activities on lawns treated with bensulide at the highest prescribed level, the aggregate MOEs may be calculated as follows:

$$\text{Adults: MOE} = \frac{5.50 \text{ mg/kg/day (NOEL)}}{0.000321 \text{ mg/kg/day (average chronic adult intake from food*)} + 3.205 \text{ mg/kg/day (dermal)}}$$

$$= 2$$

*Average intake of males 20 years and older and non-pregnant and non-nursing females 20 years and older

Children: MOE = $\frac{\text{5.50 mg/kg/day (NOEL)}}{\text{0.000627 mg/kg/day (chronic intake from food**) + 6.51 mg/kg/day (dermal)}}$

< 1

**For children 1-6 years of age

For adults pursuing low exposure activities on lawns treated with bensulide at the lowest prescribed level, or for children pursuing high exposure activities on lawns treated with bensulide at the lowest prescribed level, the aggregate MOEs may be calculated as follows:

Adults: MOE = $\frac{\text{5.50 mg/kg/day (NOEL)}}{\text{0.000321 mg/kg/day (average chronic adult intake from food*) + 0.192 mg/kg/day (dermal)}}$

= 29

*Average intake of males 20 years and older and non-pregnant and non-nursing females 20 years and older

Children: MOE = $\frac{\text{5.50 mg/kg/day (NOEL)}}{\text{0.000627 mg/kg/day (chronic intake from food**) + 3.90 mg/kg/day (dermal)}}$

= 1

**For children 1-6 years of age

All of these aggregate short-term MOEs are unacceptable, since they are far less than the value of 100, which is generally regarded as acceptable by the Agency.

5.c. Intermediate-term Aggregate Exposure and Risk (1 week to several months)

Intermediate-term (1 week to several months) aggregate exposures and risks from bensulide result from additional intermediate-term exposures, such as those resulting from repetitive exposures to bensulide-treated residential lawns or golf courses, added to the chronic exposures due to dietary routes (food). Thus, for non-workers, intermediate-term aggregate exposure and risk represent the sum of exposures and risks due to chronic dietary (food) and intermediate-term residential oral, dermal and inhalation residential exposures to bensulide. As previously discussed, the Agency believes inhalation exposures to bensulide in either residential or occupational settings are minimal. Therefore, intermediate-term aggregate exposure and risk for non-workers consist of the sum of chronic dietary exposure (via food ingestion) and additional intermediate-term dermal residential exposures. The NOEL used for intermediate-term exposures to bensulide is 0.50 mg/kg/day, based on inhibition of plasma (males and females) and brain cholinesterase (males)

activities at 4.0 mg/kg/day in a chronic toxicity study in dogs in which effects on plasma cholinesterase activities were observed as early as 13 weeks.

For adults or children pursuing high exposure activities on lawns treated with bensulide at the highest prescribed level, the aggregate MOEs may be calculated as follows:

$$\text{Adults: MOE} = \frac{0.50 \text{ mg/kg/day (NOEL)}}{0.000321 \text{ mg/kg/day (average chronic adult intake from food*)} + 0.995 \text{ mg/kg/day (dermal)}}$$

$$< 1$$

*Average intake of males 20 years and older and non-pregnant and non-nursing females 20 years and older

$$\text{Children: MOE} = \frac{0.50 \text{ mg/kg/day (NOEL)}}{0.000627 \text{ mg/kg/day (chronic intake from food**)} + 2.019 \text{ mg/kg/day (dermal)}}$$

$$< 1$$

**For children 1-6 years of age

For adults pursuing low exposure activities on lawns treated with bensulide at the lowest prescribed level, or for children pursuing high exposure activities on lawns treated with bensulide at the lowest prescribed level, the aggregate MOEs may be calculated as follows:

$$\text{Adults: MOE} = \frac{0.50 \text{ mg/kg/day (NOEL)}}{0.000321 \text{ mg/kg/day (average chronic adult intake from food*)} + 0.060 \text{ mg/kg/day (dermal)}}$$

$$= 8$$

*Average intake of males 20 years and older and non-pregnant and non-nursing females 20 years and older

$$\text{Children: MOE} = \frac{0.50 \text{ mg/kg/day (NOEL)}}{0.000627 \text{ mg/kg/day (chronic intake from food**)} + 1.211 \text{ mg/kg/day (dermal)}}$$

$$< 1$$

**For children 1-6 years of age

All of these aggregate intermediate-term MOEs are unacceptable, since they are far less than the value of 100, which is generally regarded as acceptable by the Agency.

5.d. Chronic Aggregate Exposure and Risk

A total chronic dietary risk can be estimated by adding all chronic exposures. In the case of bensulide, no chronic dermal, inhalation, or non-dietary oral non-occupational exposures were identified. Therefore, total chronic risk is the chronic risk from food. As a result of a DRES chronic exposure analysis, using 100 percent of the reassessed tolerance levels presented in Table 5 and assuming 100 percent crop treated, the following chronic aggregate risks may be calculated:

Subgroup	%RfD (food)
Non-nursing Infants (<1 year)	8
Children (1-6 years)	13
Males (20+ years)	6
Females (20+years)	7

These %RfDs are all much less than 100%, which is HED's level of concern.

6. OTHER FOOD QUALITY PROTECTION ACT CONSIDERATIONS

6.a. Cumulative Risk

Bensulide is a member of the phenyl organophosphate class of pesticides. Other members of this class include methyl parathion, ethyl parathion, and coumaphos.

Section 408(b)(2)(D)(v) of the Food Quality Protection Act requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity." The Agency believes that "available information" in this context might include not only toxicity, chemistry, and exposure data, also scientific policies and methodologies for understanding common mechanisms of toxicity and conducting cumulative risk assessments. For most pesticides, although the Agency has some information in its files that may turn out to be helpful in eventually determining whether a pesticide shares a common mechanisms of toxicity with any other substances, EPA does not at this time have the methodologies to resolve the complex scientific issues concerning common mechanism of toxicity in a meaningful way. EPA has begun a pilot process to study this issue further through the examination of particular classes of pesticides. The Agency hopes that the results of this pilot process will increase the Agency's scientific understanding of this question such that EPA will be able to develop and apply scientific principles for better determining which chemicals have a common mechanism of toxicity and evaluating the cumulative effects of such chemicals. The Agency anticipates, however, that even as its understanding of the science of common mechanisms increases, decisions on specific classes of chemicals will be heavily dependent on chemical-specific

data, much of which may not be presently available.

Although at present the Agency does not know how to apply the information in its files concerning common mechanism issues to most risk assessments, there are pesticides for which the common mechanism issues can be resolved. These pesticides include pesticides that are toxicologically dissimilar to existing chemical substances (in which case the Agency can conclude that it is unlikely that a pesticide shares a common mechanism of activity with other substances) and pesticides that produce a common toxic metabolite (in which case common mechanisms of activity will be assumed).

EPA does not have, at this time, available data to determine whether bensulide has a common mechanism of toxicity with other substances or how the include this pesticide in a cumulative risk assessment. For the purposes of reregistration, therefore, EPA has not assumed that bensulide has a common mechanism of toxicity with other substances.

6.b. Endocrine Disruption

At the present time, there are no data to indicate that exposure to bensulide would lead to endocrine disruption. However, the Agency is required to develop a screening program to determine whether certain substances (including all pesticides and inerts) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or such other endocrine effect..." The Agency is currently working with interested stakeholders, including other government agencies, public interest groups, industry and research scientists in developing a screening and testing program and a priority setting scheme to implement this program. Congress has allowed 3 years from the passage of FQPA (August 3, 1996) to implement this program. At that time, EPA may require testing of bensulide for endocrine disruptor effects.

6.c. Determination of Safety (U.S. Population, Infants, and Children)

Determination of safety includes consideration of special sensitivity to children, potential cumulative effects with pesticides that have a common mode of toxicity and aggregate risks resulting from exposure to dietary residues, residues in drinking water, and residential sources.

The database for developmental and reproductive toxicity of bensulide is considered to be complete at this time. Based on this database, the Agency has concluded that, although bensulide elicited decreased viability in second generation pups at the highest dose tested in the reproduction study, these results, when considered together with the negative results in two developmental studies, do not raise concerns regarding the adequacy of the standard uncertainty factor. Furthermore, bensulide’s primary toxic effect is the inhibition of cholinesterase activities in blood plasma, red blood cells, and brain. In addition, although there is reason to believe that effects in humans analogous to those in rats may occur at some dose level, there is no reason to believe that humans are more susceptible than rats to bensulide or to its reproductive or cholinesterase inhibitory effects. There is also no evidence to indicate that children and small infants would be more susceptible to cholinesterase inhibition by bensulide when compared with

adults.

7. DATA REQUIREMENTS

7.a. Additional Generic Data Requirements

Several issues should be discussed in a meeting with the registrant prior to defining exact data requirements. The handler issues pertain to risk mitigation options, amending existing labelling to eliminate or restrict certain exposure scenarios (e.g., greenhouse, aerial, and sod farm), and the application methods included in this assessment. Post-application issues include providing additional information pertaining to the cultural practices associated with bensulide use on agricultural crops (e.g., is there hand transplanting of crops?) and deciding on interim regulatory measures for the residential turf market as the MOEs are unacceptable (i.e., earliest at 35 days) until the *Outdoor Residential Exposure Task Force* efforts are complete.

1. Handler Studies

Identification of any pertinent data requirements are postponed by HED at this time pending discussion of risk mitigation options with the registrant. Such discussions are required because several handler exposure scenarios have MOEs that are less than 100 even though the highest level of appropriate risk mitigation was applied (i.e., personal protective equipment or engineering controls).

2. Post-Application Studies

Gowan Chemical Company has not provided any chemical-specific post-application data to support the agricultural uses of bensulide. While it is likely that the potential for post-application dermal exposure is minimal in agricultural settings due to the anticipated use patterns, Gowan should provide the EPA with a description of the cultural activities associated with the crops supported by the current bensulide labelling. Particularly, the EPA is interested in obtaining information that indicates if there are any hand labor activities in the early parts of the seasons for the labelled crops that might lead to exposures (e.g., treated soil contact due to hand transplanting to pre-plant treated fields or scouting in treated fields).

Gowan Chemical Company is a member of the ongoing *Outdoor Residential Exposure Taskforce (ORETF).* As such, studies are to be completed to enable the Agency to evaluate residential exposures due to contact with treated turf (i.e., to generate appropriate activity pattern and transfer coefficient data). Gowan must also develop a strategy to generate chemical-specific transferable residue data to be used in conjunction with the ORETF database in order for the Agency to refine the exposure/risk assessment presented in this document.

3. Product Chemistry (see Table 1.)

Supporting data are required for the analytical methods used for the quantitation of three impurities present at ≥ 0.1% (OPPTS GLN 830.1800).

Data reflecting the stability of the TGAI on exposure to metals and metal ions are required (OPPTS GLN 830.6313).

Data are required concerning UV/visible absorption for the PAI (OPPTS GLN 830.7050).

Provided that the registrant submits the data listed above and required in Table 1 for the 92% T, and either certifies that the suppliers of beginning materials and the manufacturing process for the bensulide TGAI have not changed since the last comprehensive product chemistry review or submits a complete updated product chemistry data package, HED has no objections to the reregistration of bensulide with respect to product chemistry data requirements. A tomato processing study must be submitted to fulfill the reregistration requirements for magnitude of the residue in the processed commodities of imported tomatoes.

4. Toxicology

A single-dose acute dermal toxicity study (GLN 81-2) and a repeated-dose 21-day dermal toxicity study (GLN 82-2) in which cholinesterase activities are measured in blood plasma, red blood cells, and brain must be submitted to allow a better estimate of the acute and short-term risks of dermal exposures to bensulide. HED should be consulted for guidance with respect to the protocols to be used for these studies.

The registrant must identify or submit data showing reasonable efforts were made to identify urinary metabolite "H," which represents 5.6-16.1% of the administered dose in the Unacceptable/Non-Guideline metabolism study of bensulide in rats (MRID 43335401); when this study is thus upgraded, it, together with four previous studies (MRIDs 42007901-42007904), will satisfy the guideline requirement for a metabolism study (§85-1) in rats.

7.b. Labeling Requirements for End-Use Products

1. General Requirements

The registrant must either amend product labels to restrict use to bell peppers only or generate three geographically representative field trials on non-bell peppers. In addition, the registrant must amend product labels to reflect a maximum seasonal use rate of 5 lb ai/A for carrots.

2. PPE Requirements for Pesticide Handlers

a. PPE Requirements for Occupational and Homeowner Handlers
(To be completed, pending a meeting with the registrant.)

Appendix I.

Route-to-Route Extrapolation: Conversion of inhalation dose (mg/L) to oral dose (mg/kg/day)

Male Rats:

$$\frac{1.75 \text{ mg/L} \times 1.0 \times 4 \text{ hrs/day} \times 9.60 \text{ L/hr}}{0.275 \text{ kg}} = 244.4 \text{ mg/kg/day}$$

Where:

LC_{50} = 1.75 mg/L
1.0 = Assumed absorption via inhalation
4 hrs = Exposure period in one day
9.60 = Respiratory volume (RV) for male Wistar rats
0.275 = Mean body weight of males in kg (from MRID 41646201)

Female Rats:

$$\frac{1.75 \text{ mg/L} \times 1.0 \times 4 \text{ hrs/day} \times 7.32 \text{ L/hr}}{0.233 \text{kg}} = 219.9 \text{ mg/kg/day}$$

Where:

LC_{50} = 1.75 mg/L
1.0 = Assumed absorption via inhalation
4 hrs = Exposure period in one day
7.32 = Respiratory volume (RV) for female Wistar rats
0.233 = Mean body weight of females in kg (from MRID 41646201)